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Randomised trial of mitral valve repair with leaflet resection versus leaflet preservation on functional mitral stenosis (The CAMRA CardioLink-2 Trial)

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Trial Design

Randomised trial of mitral valve repair with leaflet resection versus leaflet preservation on functional mitral stenosis (The CAMRA CardioLink-2 Trial)

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Abbreviated title: Resection vs. non-resection for repair

Word count: 4,070

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Abstract

Background The gold-standard treatment of severe mitral regurgitation (MR) due to degenerative disease is valve repair, which is surgically performed with either a leaflet resection or leaflet preservation approach. Recent data suggests that functional mitral stenosis (MS) may occur following valve repair using a leaflet resection strategy, which adversely affects patient prognosis. A randomised comparison of these two approaches to mitral repair on functional MS has not been conducted.

Methods and Analysis This is a prospective, multi-centre randomised controlled trial designed to test the hypothesis that leaflet preservation leads to better preservation of mitral valve geometry, and therefore, will be superior to leaflet resection for the primary outcome of functional MS as assessed by 12-month mean mitral valve gradient at peak exercise. Eighty-eight patients with posterior leaflet prolapse will be randomised intraoperatively once deemed by the operating surgeon to feasibly undergo mitral repair using either a leaflet resection or leaflet preservation approach. Secondary end-points include comparison of repair strategies in regards to mitral valve orifice area, leaflet coaptation height, 6-minute walk test and a composite major adverse event end-point consisting of recurrent MR≥2+, death, or hospital re-admission for congestive heart failure within 12-months of surgery.

Ethics and Dissemination Institutional ethics approval has been obtained from all enrolling sites. Overall, there remains clinical equipoise regarding the mitral valve repair strategy that is associated with the least likelihood of functional MS. This trial hopes to introduce high quality evidence to help surgical decision making in this context.

Trial Registration: clinicaltrials.gov Identifier: NCT02552771.

Abstract Word Count: 250

Keywords: Echocardiography; Mitral regurgitation; Mitral repair; Randomised controlled trial

Strengths

- Novel randomized trial comparing the two techniques used to repair degenerative mitral regurgitation
- Multi-center study
- Detailed intermediate-term postoperative echocardiographic assessment following mitral valve repair

Limitations

- Relatively small sample size
- Study includes only patients with posterior leaflet prolapse
- Study end-points will be assessed 12-months following surgery; therefore, the long-term impact of resection or non-resection based mitral repair will not be evaluated

Introduction

Mitral valve prolapse affects ~2% of individuals, and many will go on to develop severe mitral regurgitation (MR).[1-3]. These patients are generally young, healthy, and with few comorbid conditions.[1-6] The gold-standard therapy is mitral valve repair, as opposed to replacement, which restores life expectancy and improves symptoms.[4-13] The mitral valve is generally repaired with two techniques involving either leaflet resection or leaflet preservation using artificial neochordae (Figure 1).[8-13] Importantly, the decision to employ either surgical strategy is largely based on surgeon preference,[14] and data describing outcomes following mitral repair using either strategy have focused primarily on the development of recurrent MR.[6-13]

Several expert centres have reported excellent mitral valve repair rates and survival with either strategy,[4-13] but few data are available directly comparing leaflet resection with preservation techniques. In general most studies are long-term follow up single centre or surgeon experience of long term freedom from MR.[15-17] More importantly, there have been no randomised trials comparing surgical repair approaches with respect to functional mitral stenosis (MS).

Emerging data demonstrate that the presence of MS with physiological stress after repair is associated with functional limitations and heart failure even in the absence of recurrent MR.[18] In a recent study, patients who predominantly had a leaflet resection strategy had a higher peak and mitral valve gradient at peak exercise than patients who predominantly had a leaflet preservation strategy.[18] Notably, pulmonary artery systolic pressure was also lower in the latter group.[18] Differences in functional performance were observed also between groups. Patients who predominantly received a leaflet preservation strategy were able to generate more power at peak exercise and achieved a higher metabolic equivalent (MET) score. Beyond this, serum B-type natriuretic peptide (BNP) levels and Short Form (SF)-36 testing were better in patients who had a leaflet preservation strategy at the time of mitral valve repair. These data,

though prospective, were derived from a relatively small sample size, and subject to considerable selection bias, argue that mitral valve leaflet preservation may be associated with reduced functional MS and better long term outcomes.

The presence of functional MS following repair is important since mitral repair is now recommended in selected patients with minimal or no symptoms.[19 20] In spite of the widespread need and performance of mitral repair, randomised trials in this area are lacking, and surgical decision making is often driven by expertise, experience, anecdotes, and dogma. We are therefore conducting a novel, prospective randomised study comparing mitral repair of degenerative MR using either a leaflet resection or leaflet preservation approach. We hypothesise that a strategy of mitral valve leaflet preservation leads to better preservation of mitral valve geometry, and therefore, will be superior to leaflet resection for the primary outcome of functional MS as assessed by 12-month mean mitral valve gradient at peak exercise.

Methods and Analysis

Study Design Summary

This is a multi-centre, non-blinded, double-armed, randomised controlled trial comparing two different surgical strategies for repair of mitral valve prolapse. Patients will be randomly allocated 1:1 to undergo either a leaflet resection or a leaflet preservation strategy (Figure 2). Patient screening and consent will be performed by study coordinators at each of the enrolling sites.

Study End-points

The purpose of this study is to compare outcomes following repair of degenerative MR using either a leaflet resection or leaflet preservation strategy. The primary objective for this study is to compare mitral repair strategies with regards to mean mitral valve gradient at peak exercise 12-months after surgical repair of mitral valve prolapse.

The secondary objective of this study is to compare leaflet preservation and resection strategies 12-months following surgery in regards to mitral valve orifice area, age-gender predicted metabolic equivalents, mitral leaflet coaptation height, 6-minute walk test, and a composite major adverse event end-point consisting of recurrent MR ≥2+, death, or hospital re-admission for congestive heart failure within 12-months of surgery.

Study Management

This trial is funded by the Heart & Stroke Foundation (Project G-16-00014666), and the CardioLink Trial Platform at St. Michael's Hospital, Toronto, Ontario, Canada. The trial is registered at clinicaltrials.gov Identifier: NCT02552771. These funds are unrestricted therefore ultimate authority in regards to publication resides with the study authors.

All study data will be de-identified and sent to the Li Ka Shing Knowledge institute where this information will be secured stored on electronic servers. This includes echocardiographic data, which is read by the independent core echocardiographic laboratory. Access to the final study data set will be restricted to the study principal investigators (VC, SV) and the statisticians involved.

Study Population

Patients will be included in this study if they have posterior mitral valve prolapse amenable to either a leaflet resection or leaflet preservation surgical repair strategy.

Patients will be excluded if they have anterior leaflet or commissural prolapse, endocarditis or rheumatic mitral valve disease, mitral annular calcification extending beyond the circumference of one leaflet scallop, significant left ventricular (LV) dysfunction defined as a LV ejection fraction (LVEF) <40%, requiring concomitant aortic valve surgery or if they are unable to undergo bicycle ergometry.

Patients with concomitant atrial fibrillation or those who undergo a concomitant Maze procedure or bypass grafting will be included in this study.

Randomisation

Randomisation will occur intraoperatively following the initial assessment of the mitral valve with the heart arrested while supported on full cardiopulmonary bypass. Randomisation will not occur earlier as the surgeon must be sure that successful valve repair can be safely performed with either a leaflet resection or a leaflet preservation strategy.

After eligibility has been confirmed and the baseline visit assessments completed, patients will be randomly allocated in a 1:1 ratio to receive either a mitral leaflet resection or leaflet preservation surgery. Randomisation will be centralised and generated by the Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute of St. Michael's

Hospital. Randomisation will be stratified by centre using random permuted blocks of varying sizes.

Surgical Strategy

The surgical strategy will be standardised amongst the enrolling mitral surgeons/centres. All mitral valve repairs will be performed either via sternotomy or right thoracotomy with cardioplegic arrest and cardiopulmonary bypass. Only complete annuloplasty with the Carpentier-Edwards Physio II Ring (Edwards Lifesciences, Irivine, CA, USA) bands will be used and sizing will be based on the size of the anterior mitral leaflet. Closure of clefts and transfer of in situ chordae may be permitted per surgeon preference. However use of an edge-to-edge repair, either placed centrally or towards either commissure, or folding plasty will be considered protocol deviations. The leaflet resection strategy may include either a triangular or quadrangular resection with or without concomitant sliding plasty. The leaflet preservation strategy will include use of either 4-0 or 5-0 polytetrafluoroethylene sutures placed on the head of the anterolateral or posteromedial papillary muscle. Use of pledgets for placement of these neochordae on the papillary muscle will be permitted.

Echocardiographic assessment

All resting echocardiographic measurements will be performed in accordance with current guidelines.[21 22] In brief, the degree of MR following mitral repair will be assessed through calculation of the effective regurgitation orifice area as determined via the proximal isovelocity surface area method. Estimation of the diastolic pressure gradient across the mitral valve following repair will be assessed by the transmitral velocity flow curve using the simplified Bernouilli equation. Continuous wave Doppler will be used to ensure maximal velocities are recorded and Doppler gradients will be measured in the apical window. Mitral valve area will be measured using planimetry obtained on a parasternal short-axis view in mid-diastole.[22]

Additional echocardiographic measurements will be performed to assess changes in left and right ventricular size and systolic function, as per current guidelines.[21]

For stress echocardiographic assessments, patients will be securely positioned on a supine cycle ergometer table that allows for a ≤40° tilt. Patients will pedal against a fixed resistance. After an initial workload of 25 W maintained for 2 minutes, the workload will be increased stepwise by 25 W every 2 minutes. Patients will be encouraged to exercise to exhaustion.[18]

All postoperative echocardiographic assessments will be read in a blinded fashion by an independent Core laboratory based at St. Michael's Hospital, Toronto.

Study Sample Size

Stress echocardiography data following repair of degenerative MR has not been commonly reported. However, we have previously determined mean mitral gradients at peak exercise in selected patients who underwent mitral repair using a combination of leaflet preservation and resection techniques.[18 23] Based on these data and considering current valve guidelines, we propose a 5 mm Hg difference in mean mitral valve gradient at peak exercise to be clinically significant. Considering a standard deviation of 6.7 mm Hg based on our previous data,[18] 88 patients would be required to detect a difference between groups using a two-sided test with 90% power and 10% patient attrition (Table 1).

This study will be conducted at 4 tertiary-care cardiac surgery centres with a combined annual case volume of approximately 5500 operations. Of these, approximately 300 operations are for degenerative mitral regurgitation due to posterior leaflet prolapse, therefore study enrollment appears feasible to be completed within 2-years of site initiation.

Data analysis

The primary outcome and continuous secondary outcomes will be compared between groups using a Student's t-test. The composite major adverse cardiac end-point of recurrent MR ≥2+, death, or hospital re-admission for congestive heart failure within 12-months of surgery will be compared between groups using the Kaplan-Meier method. Risk factors associated with the composite end-point will also be assessed by logistic regression in order to determine the independent impact of the mitral repair strategy on outcomes. The results from the echocardiographic assessments performed 12-months following surgery will be reported to the site investigators so as to inform patient care decisions. This study is powered to tolerate a 10% patient attrition or protocol non-adherence. Therefore, if attrition exceeds 10%, more patients will be recruited to ensure adequate study power.

Study retention and safety

Study patients will be informed of the multiple postoperative assessments prior to enrollment in order to maximize study retention. Study coordinators will also work with the individual surgeon offices to ensure patient follow-up. A separate Data Safety and Monitoring Committee will evaluate surgeon and surgical site repair rates to ensure that there is no negative impact of repair intervention on clinical outcomes. This will involve review of intraoperative post-repair echocardiograms in addition to echocardiograms performed prior to hospital discharge following surgery. Nevertheless, the intervention is considered low risk given the surgical expertise an the fact that patients will be managed according to current guidelines and practice standards.[19] [20] Notwithstanding, information from the additional postoperative echocardiographic assessments will be returned to each treating surgeon's office to updated clinical status data.

Ethics and Dissemination

Mitral valve repair, as opposed to replacement, is the gold standard treatment of severe MR due to leaflet prolapse.[1-5] Although leaflet resection and leaflet preservation techniques have been well described, no randomised data is available comparing these two approaches in regards to functional MS. These data may guide clinical practice, which currently involves use of a given technique based on surgeon preference. If the hypothesis that a leaflet preservation technique results in less functional stenosis, this will lead to less leaflet resection techniques employed in mitral valve reconstruction. This may have particular relevance for young patients who undergo mitral reconstruction who are able to attain higher output states at exercise.[13 19]

In previous work performed by Chan K et al., 110 patients who underwent repair of MR due to myxomatous degeneration were divided into those that had a mean intraoperative mitral gradient ≤3 mm Hg and >3 mm Hg.[18] Patients that had a mean intraoperative gradient >3 mm Hg were predominantly treated with a resection strategy whereas patients with mean gradient ≤3 mm Hg were predominantly treated with a leaflet preservation strategy. These patients were subjected to stress echocardiography via bicycle ergometry, and serum BNP analysis, 6-minute walk test, and SF-36 assessments at a mean of 4.2±2.3 years after surgery were performed. Patients that received a predominantly leaflet resection strategy had a higher peak (24.8±10.2 versus 15.6±6.4 mm Hg, p <0.001) and mean (14.2±7.1 versus 8.9±3.8 mm Hg, p <0.001) mitral valve gradient at peak exercise compared to patients who underwent a predominantly leaflet preservation repair strategy. Notably, differences in functional performance were observed between groups. Patients who predominantly received a leaflet preservation strategy were able to generate more power at peak exercise and achieved a higher metabolic equivalent score. Beyond this, serum BNP levels and SF-36 testing was better in patients who had a leaflet preservation strategy at the time of mitral valve repair.[18] However, our work included patients who underwent mitral repair with a blend of leaflet resection and preservation strategies. Also,

patients underwent stress echocardiography and functional assessment years after surgery. Thus, although these data suggests that a mitral leaflet preservation strategy may result in less functional MS than repair with leaflet resection, this hypothesis needs validation.

This proposed randomised study represents the first trial comparing mitral repair techniques considering functional MS. Notwithstanding, there are important limitations of this trial. Patients will not be enrolled if they have complex lesions involving the anterior leaflet or MR due to non-degenerative causes. Furthermore, our primary outcome is based on echocardiographic assessments one year after surgery; therefore, the long-term durability of different repair techniques will not be assessed. Conclusions regarding the performance of resection or non-resection techniques in surgeons less familiar with mitral repair will also remain unknown.

This study involves surgeons and centres familiar with mitral valve reconstruction, thereby minimizing the risk to the patient. Also, randomisation will be performed only after the operating surgeon has deemed that successful valve repair can be performed using either leaflet resection or leaflet preservation techniques. In this study, patients will be subjected to several postoperative echocardiographic assessments, which goes beyond the structure of follow-up typically performed at most operating centres.

Overall, this proposed prospective trial will provide randomised data comparing the two widely utilized techniques for repair of degenerative MR. It is our hope that data from this trial will help guide clinical practice and the care of the numerous patients who undergo mitral reconstruction annually through the ultimate publication and presentation of the study results.

Conclusion

The findings from this study will further refine clinical mitral repair practice. As yet, there remains no randomised data to comprehensively advise surgeons as to which strategy to repair mitral prolapse, whether leaflet resection or preservation. Data from this study highlights the importance of mitral valve repair in these young patients who may experience functional limitations with an imperfect mitral reconstruction. Furthermore, it is the goal of the researchers to underscore the importance of mitral valve reconstruction in these patients.

Study Contributions

V Chan, MWA Chu, DA Latter, BE de Varennes, V Chu, TG Mesana, M Ruel, and S Verma will be performing mitral valve surgery and therefore will be involved in the randomisation and enrollment of patients. H Leong-Poi, W Tsang, and K Chan will lead the echocardiographic assessment of the patients with H Leong-Poi facilitating the independent core laboratory. KE Thorpe will perform the statistical assessments for this trial. J Hall, A Quan, N Dhingra, K Yared, KA Connelly, P Jüni and CD Mazer will be involved in study oversight, management and conduct.

Authors' Contributions to Manuscript

V. Chan and S. Verma drafted the manuscript. All authors reviewed and critically revised the manuscript; and approved the final version of the submitted manuscript.

Competing Interests Statements

M.W.A. Chu: Consultant to Edwards Lifesciences, Medtronic Canada, Livanova, and Symetis.

P. Jüni: Received research grants to the institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, and serves as unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company.

All other authors report no conflicts of interest.

References

1. Theal M, Sleik K, Anand S*, et al.* Prevalence of mitral valve prolapse in ethnic groups. *Can J Cardiol* 2004;20:511-5.
2. Freed LA, Levy D, Levine RA*, et al.* Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999;341:1-7. doi: 10.1056/NEJM199907013410101
3. Flack JM, Kvasnicka JH, Gardin JM*, et al.* Anthropometric and physiologic correlates of mitral valve prolapse in a biethnic cohort of young adults: the CARDIA study. *Am Heart J* 1999;138:486-92.
4. Chan V, Ruel M, Elmistekawy E*, et al.* Determinants of left ventricular dysfunction after repair of chronic asymptomatic mitral regurgitation. *Ann Thorac Surg* 2015;99:38-42. doi: 10.1016/j.athoracsur.2014.07.025
5. Chan V, Ruel M, Hynes M*, et al.* Impact of mitral annular calcification on early and late outcomes following mitral valve repair of myxomatous degeneration. *Interact Cardiovasc Thorac Surg* 2013;17:120-5. doi: 10.1093/icvts/ivt163
6. Chan V, Ruel M, Chaudry S*, et al.* Clinical and echocardiographic outcomes after repair of mitral valve bileaflet prolapse due to myxomatous disease. *J Thorac Cardiovasc Surg* 2012;143:S8-11. doi: 10.1016/j.jtcvs.2012.01.046
7. Castillo JG, Anyanwu AC, Fuster V*, et al.* A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. *J Thorac Cardiovasc Surg* 2012;144:308-12. doi: 10.1016/j.jtcvs.2011.12.054
8. Carpentier A. Cardiac valve surgery--the "French correction". *J Thorac Cardiovasc Surg* 1983;86:323-37.
9. Braunberger E, Deloche A, Berrebi A*, et al.* Very long-term results (more than 20 years) of valve repair with carpentier's techniques in nonrheumatic mitral valve insufficiency. *Circulation* 2001;104:I8-11.

10. Filsoufi F, Carpentier A. Principles of reconstructive surgery in degenerative mitral valve disease. *Semin Thorac Cardiovasc Surg* 2007;19:103-10. doi: 10.1053/j.semtcvs.2007.04.003

11. Ling LH, Enriquez-Sarano M, Seward JB*, et al.* Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996;335:1417-23. doi: 10.1056/NEJM199611073351902

12. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D*, et al.* Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005;352:875-83. doi: 10.1056/NEJMoa041451

13. Verma S, Mesana TG. Mitral-valve repair for mitral-valve prolapse. *N Engl J Med* 2009;361:2261-9. doi: 10.1056/NEJMct0806111

14. Gammie JS, Sheng S, Griffith BP*, et al.* Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg* 2009;87:1431-7; discussion 37-9. doi: 10.1016/j.athoracsur.2009.01.064

15. Seeburger J, Falk V, Borger MA*, et al.* Chordae replacement versus resection for repair of isolated posterior mitral leaflet prolapse: a egalite. *Ann Thorac Surg* 2009;87:1715-20. doi: 10.1016/j.athoracsur.2009.03.003

16. Falk V, Seeburger J, Czesla M*, et al.* How does the use of polytetrafluoroethylene neochordae for posterior mitral valve prolapse (loop technique) compare with leaflet resection? A prospective randomized trial. *J Thorac Cardiovasc Surg* 2008;136:1205; discussion 05-6. doi: 10.1016/j.jtcvs.2008.07.028

17. Lange R, Guenther T, Noebauer C*, et al.* Chordal replacement versus quadrangular resection for repair of isolated posterior mitral leaflet prolapse. *Ann Thorac Surg* 2010;89:1163-70; discussion 70. doi: 10.1016/j.athoracsur.2009.12.057

18. Chan KL, Chen SY, Chan V*, et al.* Functional significance of elevated mitral gradients after repair for degenerative mitral regurgitation. *Circ Cardiovasc Imaging* 2013;6:1041-7. doi: 10.1161/CIRCIMAGING.112.000688

19. Nishimura RA, Otto CM, Bonow RO, *et al.* 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Thorac Cardiovasc Surg* 2014;148:e1-e132. doi: 10.1016/j.jtcvs.2014.05.014

20. Vahanian A, Alfieri O, Andreotti F, *et al.* Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;42:S1-44. doi: 10.1093/ejcts/ezs455

21. Lang RM, Badano LP, Mor-Avi V, *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39 e14. doi: 10.1016/j.echo.2014.10.003

22. Baumgartner H, Hung J, Bermejo J, *et al.* Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;22:1-23; quiz 101-2. doi: 10.1016/j.echo.2008.11.029

23. Mesana TG, Lam BK, Chan V, *et al.* Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: potential affect on surgical strategy. *J Thorac Cardiovasc Surg* 2013;146:1418-23; discussion 23-5. doi: 10.1016/j.jtcvs.2013.08.011

Table 1: Study Sample Size Estimates

	0% Attrition	5% Attrition	10% Attrition
Power = 90% Two-tailed	78 (39 per group)	84 (42 per group)	88 (44 per group)
Power = 80% Two-tailed	60 (30 per group)	64 (32 per group)	68 (34 per group)

Figure Legends

Figure 1: Mitral valve repair using leaflet resection and leaflet preservation techniques. **A:** Prolapse of the posterior leaflet of the mitral valve. **B-D:** Quadrangular resection of the prolapsing scallop, annular plication and subsequent reconstruction of the remaining lateral and medial edges of the posterior leaflet. **E-G:** Valve repair with leaflet preservation via placement of artificial neochordae from the papillary muscles to the prolapsing leaflet edge.

Figure 2: Study Schematic. Patients will be assessed clinically and echocardiographically prior to hospital discharge and 1-year following mitral valve reconstruction.

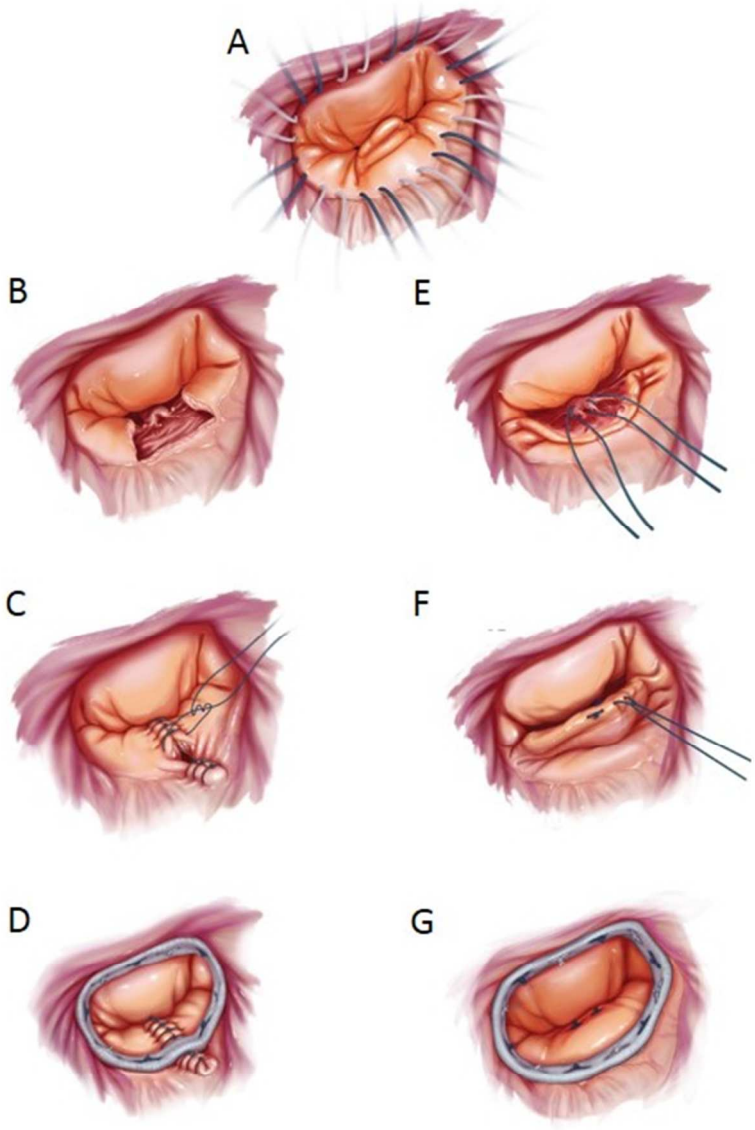

Figure 1: Mitral valve repair using leaflet resection and leaflet preservation techniques. A: Prolapse of the posterior leaflet of the mitral valve. B-D: Quadrangular resection of the prolapsing scallop, annular plication and subsequent reconstruction of the remaining lateral and medial edges of the posterior leaflet. E-G: Valve repair with leaflet preservation via placement of artificial neochordae from the papillary muscles to the prolapsing leaflet edge.
Figure 1
3448x4597mm (4 x 4 DPI)

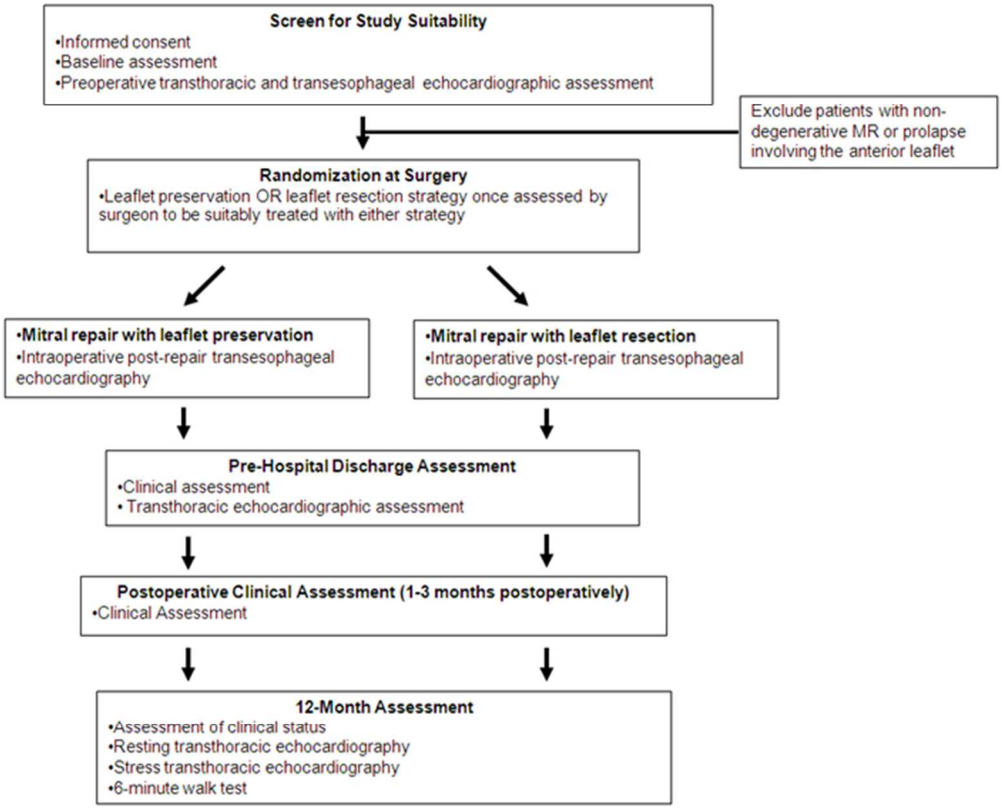

Figure 2: Study Schematic. Patients will be assessed clinically and echocardiographically prior to hospital discharge and 1-year following mitral valve reconstruction.
Figure 2
248x204mm (72 x 72 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,6
	2b	All items from the World Health Organization Trial Registration Data Set	1,2,6-9, 14
Protocol version	3	Date and version identifier	Ver 5; Oct 3, 2016
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6-7
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9,Fig 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9, Table 1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9, Table 1
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11-12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11-12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11-12
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Ver 4; Oct 3, 2016
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Randomised trial of mitral valve repair with leaflet resection versus leaflet preservation on functional mitral stenosis (The CAMRA CardioLink-2 Trial)

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Trial Design

Randomised trial of mitral valve repair with leaflet resection versus leaflet preservation on functional mitral stenosis (The CAMRA CardioLink-2 Trial)

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Abbreviated title: Resection vs. non-resection for repair

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Abstract

Background The gold-standard treatment of severe mitral regurgitation (MR) due to degenerative disease is valve repair, which is surgically performed with either a leaflet resection or leaflet preservation approach. Recent data suggests that functional mitral stenosis (MS) may occur following valve repair using a leaflet resection strategy, which adversely affects patient prognosis. A randomised comparison of these two approaches to mitral repair on functional MS has not been conducted.

Methods and Analysis This is a prospective, multi-centre randomised controlled trial designed to test the hypothesis that leaflet preservation leads to better preservation of mitral valve geometry, and therefore, will be superior to leaflet resection for the primary outcome of functional MS as assessed by 12-month mean mitral valve gradient at peak exercise. Eighty-eight patients with posterior leaflet prolapse will be randomised intraoperatively once deemed by the operating surgeon to feasibly undergo mitral repair using either a leaflet resection or leaflet preservation approach. Secondary end-points include comparison of repair strategies in regards to mitral valve orifice area, leaflet coaptation height, 6-minute walk test and a composite major adverse event end-point consisting of recurrent MR≥2+, death, or hospital re-admission for congestive heart failure within 12-months of surgery.

Ethics and Dissemination Institutional ethics approval has been obtained from all enrolling sites. Overall, there remains clinical equipoise regarding the mitral valve repair strategy that is associated with the least likelihood of functional MS. This trial hopes to introduce high quality evidence to help surgical decision making in this context.

Trial Registration: clinicaltrials.gov Identifier: NCT02552771.

Abstract Word Count: 250

Keywords: Echocardiography; Mitral regurgitation; Mitral repair; Randomised controlled trial

Strengths

- Novel randomized trial comparing the two techniques used to repair degenerative mitral regurgitation
- Multi-center study
- Detailed intermediate-term postoperative echocardiographic assessment following mitral valve repair

Limitations

- Relatively small sample size
- Study includes only patients with posterior leaflet prolapse
- Study end-points will be assessed 12-months following surgery; therefore, the long-term impact of resection or non-resection based mitral repair will not be evaluated

Introduction

Mitral valve prolapse affects ~2% of individuals, and many will go on to develop severe mitral regurgitation (MR).[1-3]. These patients are generally young, healthy, and with few comorbid conditions.[1-6] The gold-standard therapy is mitral valve repair, as opposed to replacement, which restores life expectancy and improves symptoms.[4-13] The mitral valve is generally repaired with two techniques involving either leaflet resection or leaflet preservation using artificial neochordae (Figure 1).[8-13] Importantly, the decision to employ either surgical strategy is largely based on surgeon preference,[14] and data describing outcomes following mitral repair using either strategy have focused primarily on the development of recurrent MR.[6-13]

Several expert centres have reported excellent mitral valve repair rates and survival with either strategy,[4-13] but few data are available directly comparing leaflet resection with preservation techniques. In general most studies are long-term follow up single centre or surgeon experience of long term freedom from MR.[15-17] More importantly, there have been no randomised trials comparing surgical repair approaches with respect to functional mitral stenosis (MS).

Emerging data demonstrate that the presence of MS with physiological stress after repair is associated with functional limitations and heart failure even in the absence of recurrent MR.[18] In a recent study, patients who predominantly had a leaflet resection strategy had a higher peak and mitral valve gradient at peak exercise than patients who predominantly had a leaflet preservation strategy.[18] Notably, pulmonary artery systolic pressure was also lower in the latter group.[18] Differences in functional performance were observed also between groups. Patients who predominantly received a leaflet preservation strategy were able to generate more power at peak exercise and achieved a higher metabolic equivalent (MET) score. Beyond this, serum B-type natriuretic peptide (BNP) levels and Short Form (SF)-36 testing were better in patients who had a leaflet preservation strategy at the time of mitral valve repair. These data,

though prospective, were derived from a relatively small sample size, and subject to considerable selection bias, argue that mitral valve leaflet preservation may be associated with reduced functional MS and better long term outcomes.

The presence of functional MS following repair is important since mitral repair is now recommended in selected patients with minimal or no symptoms.[19 20] In spite of the widespread need and performance of mitral repair, randomised trials in this area are lacking, and surgical decision making is often driven by expertise, experience, anecdotes, and dogma. We are therefore conducting a novel, prospective randomised study comparing mitral repair of degenerative MR using either a leaflet resection or leaflet preservation approach. We hypothesise that a strategy of mitral valve leaflet preservation leads to better preservation of mitral valve geometry, and therefore, will be superior to leaflet resection for the primary outcome of functional MS as assessed by 12-month mean mitral valve gradient at peak exercise.

Methods and Analysis

Study Design Summary

This is a multi-centre, non-blinded, double-armed, randomised controlled trial comparing two different surgical strategies for repair of mitral valve prolapse. Patients will be randomly allocated 1:1 to undergo either a leaflet resection or a leaflet preservation strategy (Figure 2). Patient screening and consent will be performed by study coordinators at each of the enrolling sites.

Study End-points

The purpose of this study is to compare outcomes following repair of degenerative MR using either a leaflet resection or leaflet preservation strategy. The primary objective for this study is to compare mitral repair strategies with regards to mean mitral valve gradient at peak exercise 12-months after surgical repair of mitral valve prolapse.

The secondary objective of this study is to compare leaflet preservation and resection strategies 12-months following surgery in regards to mitral valve orifice area, age-gender predicted metabolic equivalents, mitral leaflet coaptation height, 6-minute walk test, and a composite major adverse event end-point consisting of recurrent MR ≥2+, death, or hospital re-admission for congestive heart failure within 12-months of surgery.

Study Management

This trial is funded by the Heart & Stroke Foundation (Project G-16-00014666), and the CardioLink Trial Platform at St. Michael's Hospital, Toronto, Ontario, Canada. The trial is registered at clinicaltrials.gov Identifier: NCT02552771. These funds are unrestricted therefore ultimate authority in regards to publication resides with the study authors.

All study data will be de-identified and sent to the Li Ka Shing Knowledge institute where this information will be secured stored on electronic servers. This includes echocardiographic data, which is read by the independent core echocardiographic laboratory. Access to the final study data set will be restricted to the study principal investigators (VC, SV) and the statisticians involved.

Study Population

Patients will be included in this study if they have posterior mitral valve prolapse amenable to either a leaflet resection or leaflet preservation surgical repair strategy.

Patients will be excluded if they have anterior leaflet or commissural prolapse, endocarditis or rheumatic mitral valve disease, mitral annular calcification extending beyond the circumference of one leaflet scallop, significant left ventricular (LV) dysfunction defined as a LV ejection fraction (LVEF) <40%, requiring concomitant aortic valve surgery or if they are unable to undergo bicycle ergometry.

Patients with concomitant atrial fibrillation or those who undergo a concomitant Maze procedure or bypass grafting will be included in this study.

Randomisation

Randomisation will occur intraoperatively following the initial assessment of the mitral valve with the heart arrested while supported on full cardiopulmonary bypass. Randomisation will not occur earlier as the surgeon must be sure that successful valve repair can be safely performed with either a leaflet resection or a leaflet preservation strategy.

After eligibility has been confirmed and the baseline visit assessments completed, patients will be randomly allocated in a 1:1 ratio to receive either a mitral leaflet resection or leaflet preservation surgery. Randomisation will be centralised and generated by the Applied Health Research Centre (AHRC) at the Li Ka Shing Knowledge Institute of St. Michael's

Hospital. Randomisation will be stratified by centre using random permuted blocks of varying sizes.

Surgical Strategy

The surgical strategy will be standardised amongst the enrolling mitral surgeons/centres. All mitral valve repairs will be performed either via sternotomy or right thoracotomy with cardioplegic arrest and cardiopulmonary bypass. Only complete annuloplasty with the Carpentier-Edwards Physio II Ring (Edwards Lifesciences, Irivine, CA, USA) bands will be used and sizing will be based on the size of the anterior mitral leaflet. Closure of clefts and transfer of in situ chordae may be permitted per surgeon preference. However use of an edge-to-edge repair, either placed centrally or towards either commissure, or folding plasty will be considered protocol deviations. The leaflet resection strategy may include either a triangular or quadrangular resection with or without concomitant sliding plasty. The leaflet preservation strategy will include use of either 4-0 or 5-0 polytetrafluoroethylene sutures placed on the head of the anterolateral or posteromedial papillary muscle. Use of pledgets for placement of these neochordae on the papillary muscle will be permitted.

Echocardiographic assessment

All resting echocardiographic measurements will be performed in accordance with current guidelines.[21 22] In brief, the degree of MR following mitral repair will be assessed through calculation of the effective regurgitation orifice area as determined via the proximal isovelocity surface area method. Estimation of the diastolic pressure gradient across the mitral valve following repair will be assessed by the transmitral velocity flow curve using the simplified Bernouilli equation. Continuous wave Doppler will be used to ensure maximal velocities are recorded and Doppler gradients will be measured in the apical window. Mitral valve area will be measured using planimetry obtained on a parasternal short-axis view in mid-diastole and also

via the continuity method.[22] Additional echocardiographic measurements will be performed to assess changes in left and right ventricular size and systolic function, as per current guidelines.[21]

For stress echocardiographic assessments, patients will be securely positioned on a supine cycle ergometer table that allows for a ≤40° tilt. Patients will pedal against a fixed resistance. After an initial workload of 25 W maintained for 2 minutes, the workload will be increased stepwise by 25 W every 2 minutes. Patients will be encouraged to exercise to exhaustion.[18]

All postoperative echocardiographic assessments will be read in a blinded fashion by an independent Core laboratory based at St. Michael's Hospital, Toronto.

Study Sample Size

Stress echocardiography data following repair of degenerative MR has not been commonly reported. However, we have previously determined mean mitral gradients at peak exercise in selected patients who underwent mitral repair using a combination of leaflet preservation and resection techniques.[18 23] Based on these data and considering current valve guidelines, we propose a 5 mm Hg difference in mean mitral valve gradient at peak exercise to be clinically significant. Considering a standard deviation of 6.7 mm Hg based on our previous data,[18] 88 patients would be required to detect a difference between groups using a two-sided test with 5% alpha, 90% power and 10% patient attrition (Table 1).

This study will be conducted at 4 tertiary-care cardiac surgery centres with a combined annual case volume of approximately 5500 operations. Of these, approximately 300 operations are for degenerative mitral regurgitation due to posterior leaflet prolapse, therefore study enrollment appears feasible to be completed within 2-years of site initiation.

Data analysis

Baseline characteristics will be compared between groups using a chi-square test for categorical variables or a Student's t-test for continuous variables. The primary outcome and continuous secondary outcomes will be compared between groups using a Student's t-test. The treatment effect will be expressed as the mean difference between groups with 95% confidence interval. Missing data for the primary outcome is unlikely to be missing at random and so standard imputation approaches are problematic. Therefore two analyses will be conducted if the primary outcome is missing in more than 5% of the randomised subjects. The first will be the usual complete case analysis. The second will employ inverse probability weighting on the probability of "completing" the study. If these analyses are concordant, the simpler analysis will be primary. The proportion of individuals experiencing the composite major adverse cardiac end-point of recurrent MR ≥2+, death, or hospital re-admission for congestive heart failure within 12-months of surgery will be compared between groups using method chi-square test. Risk factors associated with the composite end-point will also be assessed by logistic regression in order to determine the adjusted impact of the mitral repair strategy on outcomes. A two-sided significance level of 5% will be used throughout. Statistical analysis will be performed using R.[24] The results from the echocardiographic assessments performed 12-months following surgery will be reported to the site investigators so as to inform patient care decisions. This study is powered to tolerate a 10% patient attrition or protocol non-adherence. Therefore, if attrition exceeds 10%, more patients will be recruited to ensure adequate study power.

In addition to the reporting of study end-points, the overall number of patients undergoing repair of degenerative MR at each treatment center will be reported in order to better provide context of the findings of the study.

Study retention and safety

Study patients will be informed of the multiple postoperative assessments prior to enrollment in order to maximize study retention. Study coordinators will also work with the individual surgeon offices to ensure patient follow-up. A separate Data Safety and Monitoring Committee will evaluate surgeon and surgical site repair rates to ensure that there is no negative impact of repair intervention on clinical outcomes. This will involve review of intraoperative post-repair echocardiograms in addition to echocardiograms performed prior to hospital discharge following surgery. Nevertheless, the intervention is considered low risk given the surgical expertise an the fact that patients will be managed according to current guidelines and practice standards.[19] [20] Notwithstanding, information from the additional postoperative echocardiographic assessments will be returned to each treating surgeon's office to updated clinical status data.

Ethics and Dissemination

Mitral valve repair, as opposed to replacement, is the gold standard treatment of severe MR due to leaflet prolapse.[1-5] Although leaflet resection and leaflet preservation techniques have been well described, no randomised data is available comparing these two approaches in regards to functional MS. These data may guide clinical practice, which currently involves use of a given technique based on surgeon preference. If the hypothesis that a leaflet preservation technique results in less functional stenosis, this will lead to less leaflet resection techniques employed in mitral valve reconstruction. This may have particular relevance for young patients who undergo mitral reconstruction who are able to attain higher output states at exercise.[13 19]

In previous work performed by Chan K et al., 110 patients who underwent repair of MR due to myxomatous degeneration were divided into those that had a mean intraoperative mitral gradient ≤3 mm Hg and >3 mm Hg.[18] Patients with a higher mean trans-mitral repair gradient were more likely to undergo leaflet resection with annular plication.. These patients were subjected to stress echocardiography via bicycle ergometry, and serum BNP analysis, 6-minute walk test, and SF-36 assessments at a mean of 4.2±2.3 years after surgery were performed. Patients that received a predominantly leaflet resection strategy had a higher peak (24.8±10.2 versus 15.6±6.4 mm Hg, p <0.001) and mean (14.2±7.1 versus 8.9±3.8 mm Hg, p <0.001) mitral valve gradient at peak exercise compared to patients who underwent a predominantly leaflet preservation repair strategy. Notably, differences in functional performance were observed between groups. Patients who predominantly received a leaflet preservation strategy were able to generate more power at peak exercise and achieved a higher metabolic equivalent score. Beyond this, serum BNP levels and SF-36 testing was better in patients who had a leaflet preservation strategy at the time of mitral valve repair.[18] However, our work included patients who underwent mitral repair with a blend of leaflet resection and preservation strategies. Also, patients underwent stress echocardiography and functional assessment years after surgery.

Thus, although these data suggests that a mitral leaflet preservation strategy may result in less functional MS than repair with leaflet resection, this hypothesis needs validation.

This proposed randomised study represents the first trial comparing mitral repair techniques considering functional MS. Notwithstanding, there are important limitations of this trial. Patients will not be enrolled if they have complex lesions involving the anterior leaflet or MR due to non-degenerative causes. Furthermore, our primary outcome is based on echocardiographic assessments one year after surgery; therefore, the long-term durability of different repair techniques will not be assessed. Conclusions regarding the performance of resection or non-resection techniques in surgeons less familiar with mitral repair will also remain unknown.

This study involves surgeons and centres familiar with mitral valve reconstruction, thereby minimizing the risk to the patient.[6] Also, randomisation will be performed only after the operating surgeon has deemed that successful valve repair can be performed using either leaflet resection or leaflet preservation techniques. In this study, patients will be subjected to several postoperative echocardiographic assessments, which goes beyond the structure of follow-up typically performed at most operating centres.

Overall, this proposed prospective trial will provide randomised data comparing the two widely utilized techniques for repair of degenerative MR. It is our hope that data from this trial will help guide clinical practice and the care of the numerous patients who undergo mitral reconstruction annually through the ultimate publication and presentation of the study results.

Conclusion

The findings from this study will further refine clinical mitral repair practice. As yet, there remains no randomised data to comprehensively advise surgeons as to which strategy to repair mitral prolapse, whether leaflet resection or preservation. Data from this study highlights the importance of mitral valve repair in these young patients who may experience functional limitations with an imperfect mitral reconstruction. Furthermore, it is the goal of the researchers to underscore the importance of mitral valve reconstruction in these patients.

Study Contributions

V Chan, MWA Chu, DA Latter, BE de Varennes, V Chu, TG Mesana, M Ruel, and S Verma will be performing mitral valve surgery and therefore will be involved in the randomisation and enrollment of patients. H Leong-Poi, W Tsang, and K Chan will lead the echocardiographic assessment of the patients with H Leong-Poi facilitating the independent core laboratory. KE Thorpe will perform the statistical assessments for this trial. J Hall, A Quan, N Dhingra, K Yared, H Teoh, KA Connelly, P Jüni and CD Mazer will be involved in study oversight, management and conduct.

Authors' Contributions to Manuscript

V. Chan and S. Verma drafted the manuscript. All authors reviewed and critically revised the manuscript; and approved the final version of the submitted manuscript.

Competing Interests Statements

M.W.A. Chu: Consultant to Edwards Lifesciences, Medtronic Canada, Livanova, and Symetis.

P. Jüni: Received research grants to the institution from AstraZeneca, Biotronik, Biosensors International, Eli Lilly and The Medicines Company, and serves as unpaid member of the steering group of trials funded by AstraZeneca, Biotronik, Biosensors, St. Jude Medical and The Medicines Company.

All other authors report no conflicts of interest.

References

1. Theal M, Sleik K, Anand S*, et al.* Prevalence of mitral valve prolapse in ethnic groups. *Can J Cardiol* 2004;20:511-5.
2. Freed LA, Levy D, Levine RA*, et al.* Prevalence and clinical outcome of mitral-valve prolapse. *N Engl J Med* 1999;341:1-7. doi: 10.1056/NEJM199907013410101
3. Flack JM, Kvasnicka JH, Gardin JM*, et al.* Anthropometric and physiologic correlates of mitral valve prolapse in a biethnic cohort of young adults: the CARDIA study. *Am Heart J* 1999;138:486-92.
4. Chan V, Ruel M, Elmistekawy E*, et al.* Determinants of left ventricular dysfunction after repair of chronic asymptomatic mitral regurgitation. *Ann Thorac Surg* 2015;99:38-42. doi: 10.1016/j.athoracsur.2014.07.025
5. Chan V, Ruel M, Hynes M*, et al.* Impact of mitral annular calcification on early and late outcomes following mitral valve repair of myxomatous degeneration. *Interact Cardiovasc Thorac Surg* 2013;17:120-5. doi: 10.1093/icvts/ivt163
6. Chan V, Ruel M, Chaudry S*, et al.* Clinical and echocardiographic outcomes after repair of mitral valve bileaflet prolapse due to myxomatous disease. *J Thorac Cardiovasc Surg* 2012;143:S8-11. doi: 10.1016/j.jtcvs.2012.01.046
7. Castillo JG, Anyanwu AC, Fuster V*, et al.* A near 100% repair rate for mitral valve prolapse is achievable in a reference center: implications for future guidelines. *J Thorac Cardiovasc Surg* 2012;144:308-12. doi: 10.1016/j.jtcvs.2011.12.054
8. Carpentier A. Cardiac valve surgery--the "French correction". *J Thorac Cardiovasc Surg* 1983;86:323-37.
9. Braunberger E, Deloche A, Berrebi A*, et al.* Very long-term results (more than 20 years) of valve repair with carpentier's techniques in nonrheumatic mitral valve insufficiency. *Circulation* 2001;104:I8-11.
10. Filsoufi F, Carpentier A. Principles of reconstructive surgery in degenerative mitral valve disease. *Semin Thorac Cardiovasc Surg* 2007;19:103-10. doi: 10.1053/j.semtcvs.2007.04.003
11. Ling LH, Enriquez-Sarano M, Seward JB*, et al.* Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med* 1996;335:1417-23. doi: 10.1056/NEJM199611073351902
12. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D*, et al.* Quantitative determinants of the outcome of asymptomatic mitral regurgitation. *N Engl J Med* 2005;352:875-83. doi: 10.1056/NEJMoa041451
13. Verma S, Mesana TG. Mitral-valve repair for mitral-valve prolapse. *N Engl J Med* 2009;361:2261-9. doi: 10.1056/NEJMct0806111
14. Gammie JS, Sheng S, Griffith BP*, et al.* Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg* 2009;87:1431-7; discussion 37-9. doi: 10.1016/j.athoracsur.2009.01.064
15. Seeburger J, Falk V, Borger MA*, et al.* Chordae replacement versus resection for repair of isolated posterior mitral leaflet prolapse: a egalite. *Ann Thorac Surg* 2009;87:1715-20. doi: 10.1016/j.athoracsur.2009.03.003
16. Falk V, Seeburger J, Czesla M*, et al.* How does the use of polytetrafluoroethylene neochordae for posterior mitral valve prolapse (loop technique) compare with leaflet resection? A prospective randomized trial. *J Thorac Cardiovasc Surg* 2008;136:1205; discussion 05-6. doi: 10.1016/j.jtcvs.2008.07.028
17. Lange R, Guenther T, Noebauer C*, et al.* Chordal replacement versus quadrangular resection for repair of isolated posterior mitral leaflet prolapse. *Ann Thorac Surg* 2010;89:1163-70; discussion 70. doi: 10.1016/j.athoracsur.2009.12.057

18. Chan KL, Chen SY, Chan V*, et al.* Functional significance of elevated mitral gradients after repair for degenerative mitral regurgitation. *Circ Cardiovasc Imaging* 2013;6:1041-7. doi: 10.1161/CIRCIMAGING.112.000688
19. Nishimura RA, Otto CM, Bonow RO*, et al.* 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Thorac Cardiovasc Surg* 2014;148:e1-e132. doi: 10.1016/j.jtcvs.2014.05.014
20. Vahanian A, Alfieri O, Andreotti F*, et al.* Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg* 2012;42:S1-44. doi: 10.1093/ejcts/ezs455
21. Lang RM, Badano LP, Mor-Avi V*, et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;28:1-39 e14. doi: 10.1016/j.echo.2014.10.003
22. Baumgartner H, Hung J, Bermejo J*, et al.* Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. *J Am Soc Echocardiogr* 2009;22:1-23; quiz 101-2. doi: 10.1016/j.echo.2008.11.029
23. Mesana TG, Lam BK, Chan V*, et al.* Clinical evaluation of functional mitral stenosis after mitral valve repair for degenerative disease: potential affect on surgical strategy. *J Thorac Cardiovasc Surg* 2013;146:1418-23; discussion 23-5. doi: 10.1016/j.jtcvs.2013.08.011
24. R: A language and environment for statistical computing [program]. Vienna, Austria: R Foundation for Statistical Computing, Available from: https://www.R-project.org/ 2016.

Table 1: Study Sample Size Estimates

	0% Attrition	5% Attrition	10% Attrition
Power = 90% Two-tailed	78 (39 per group)	84 (42 per group)	88 (44 per group)
Power = 80% Two-tailed	60 (30 per group)	64 (32 per group)	68 (34 per group)

Figure Legends

Figure 1: Mitral valve repair using leaflet resection and leaflet preservation techniques. **A:** Prolapse of the posterior leaflet of the mitral valve. **B-D:** Quadrangular resection of the prolapsing scallop, annular plication and subsequent reconstruction of the remaining lateral and medial edges of the posterior leaflet. **E-G:** Valve repair with leaflet preservation via placement of artificial neochordae from the papillary muscles to the prolapsing leaflet edge.

Figure 2: Study Schematic. Patients will be assessed clinically and echocardiographically prior to hospital discharge and 1-year following mitral valve reconstruction.

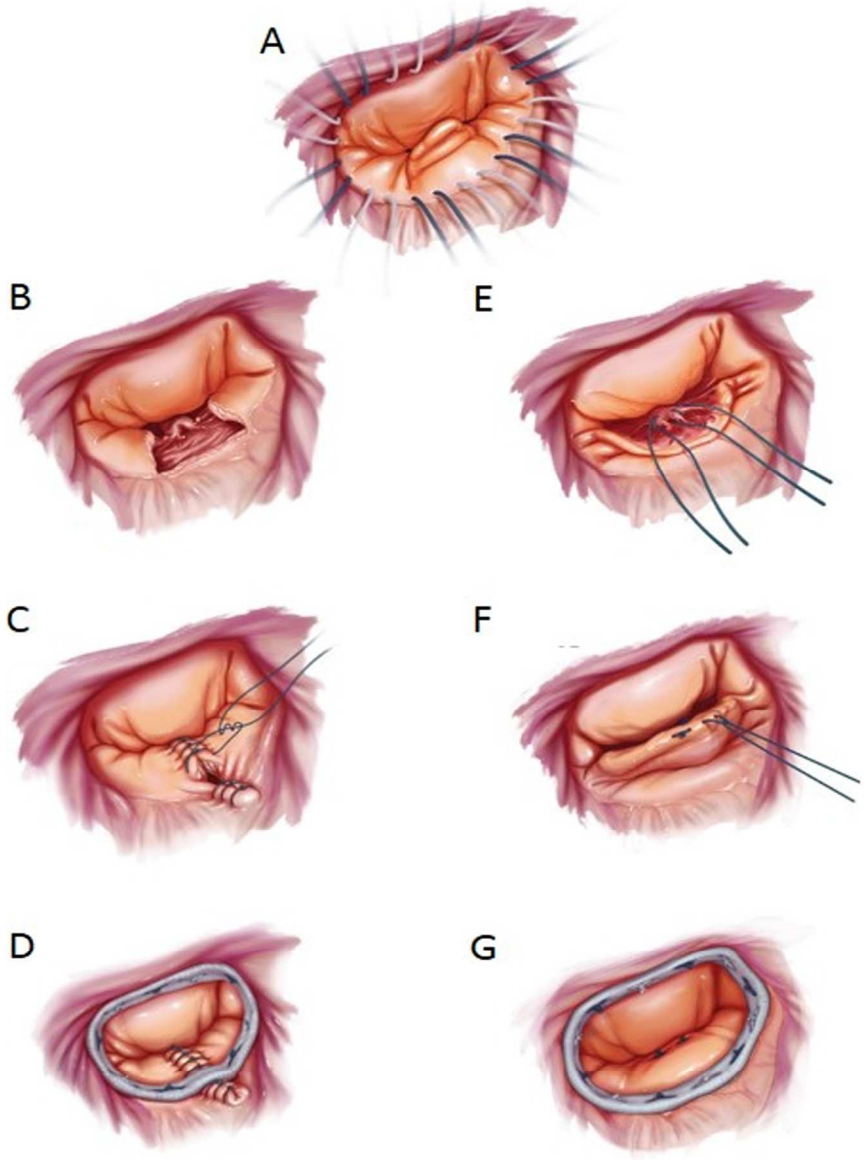

Figure 1: Mitral valve repair using leaflet resection and leaflet preservation techniques. A: Prolapse of the posterior leaflet of the mitral valve. B-D: Quadrangular resection of the prolapsing scallop, annular plication and subsequent reconstruction of the remaining lateral and medial edges of the posterior leaflet. E-G: Valve repair with leaflet preservation via placement of artificial neochordae from the papillary muscles to the prolapsing leaflet edge.

338x468mm (300 x 300 DPI)

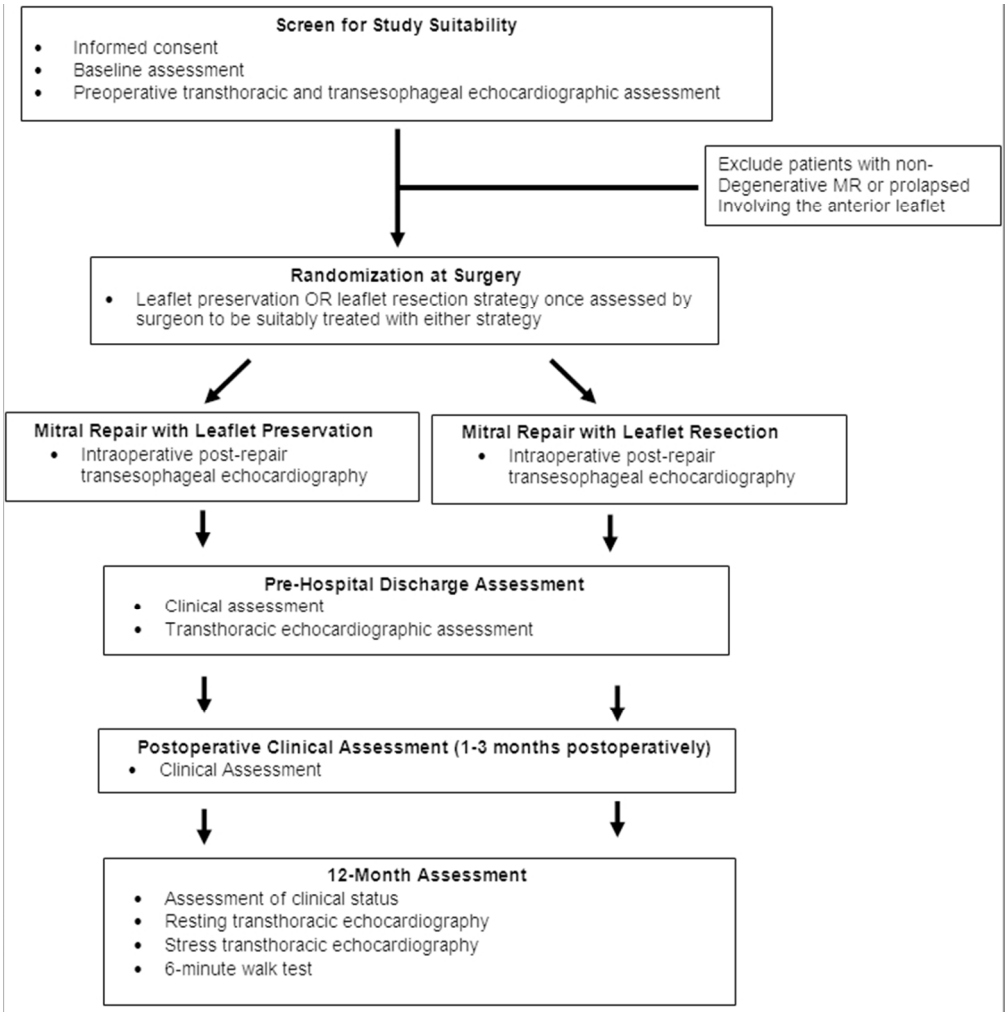

Figure 2: Study Schematic. Patients will be assessed clinically and echocardiographically prior to hospital discharge and 1-year following mitral valve reconstruction.

64x65mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2,6
	2b	All items from the World Health Organization Trial Registration Data Set	1,2,6-9, 14
Protocol version	3	Date and version identifier	Ver 5; Oct 3, 2016
Funding	4	Sources and types of financial, material, and other support	6
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	6
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	6-7
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Not applicable

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-6
	6b	Explanation for choice of comparators	4-6
Objectives	7	Specific objectives or hypotheses	5-6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6-7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not applicable
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not applicable
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Not applicable
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8-9,Fig 2

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9, Table 1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9, Table 1
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7-8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7-8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7-8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not applicable
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Not applicable
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9-10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not applicable
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	Not applicable
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	11-12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	11-12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	6
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	7
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	7
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not applicable
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11-12
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not applicable
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Ver 4; Oct 3, 2016
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.