2017

Outcomes of a Novel Approach to Transcatheter and Hybrid Pulmonary Valve Replacement for Congenital Heart Disease in a Single Center

Marion E. McRae
Medical University of South Carolina

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Marion E. McRae

A dissertation submitted to the faculty of the Medical University of South Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the College of Nursing.

December 2017

Approved by:

Teresa J. Kelechi PhD, RN, FAAN Chair, Advisory Committee

Martina Mueller PhD

Bernice Coleman PhD, ACNP-BC, FAHA, FAAN

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Acknowledgements

I would like to express my gratitude to my committee chair Dr. Teresa Kelechi and my committee members Dr. Martina Mueller and Dr. Bernice Coleman for their support and guidance through the dissertation process. I am extremely grateful to Dr. Linda Burnes Bolton, Chief Nursing Executive at Cedars-Sinai Health Center who ensured that I had the financial and work support to complete this degree. This work would not have been possible without the support of the Future of Nursing Scholar Award from the Robert Wood Johnson Foundation (Princeton, NJ) and Cedars-Sinai Medical Center (Los Angeles, CA). Lastly, this work is dedicated to my late parents James M. and Madeline E. McRae who never had the opportunity to pursue a university education but instilled in me the value of an education and funded my early educational endeavors. There were many obstacles along the way to a doctoral degree but I persisted because I knew they expected me to succeed and would accept no less.

Abstract

Purpose: This dissertation was designed to build my expertise in working with large datasets and to apply that knowledge to congenital heart disease patient problems. Relationships in a large dataset were examined using a nursing theory approach to identify relationships that would benefit from further research as a preliminary skill-building step. Outcomes from transcatheter (TC) and hybrid pulmonary valve replacement (PVR) versus surgical PVR were explored in the literature and finally in a study to begin to provide information to help health care providers tailor education and recommendations to patients/families selecting a treatment strategy for pulmonary regurgitation and/or stenosis.

Design: A quasi-meta-analysis (Manuscript I) was undertaken to compare outcomes from TC and surgical PVR using the Wilson and Cleary (1995) conceptual model of health-related quality of life (HRQOL). In Manuscript II the Omaha System was used to analyze data from an existing leg ulcer database (no appropriate congenital heart disease database was available) to increase my skills at handling large databases and applying nursing theory to identify relationships that would benefit from further research. Visualization techniques (heat maps) were then used to examine new relationships among the variables. Models were developed to test the relationships between variables in predicting adherence to leg ulcer treatment and predicting leg ulcer development. Gaps identified in the literature from Manuscript I and the skills learned from the Manuscript II project were then used to design a single-center study to examine TC (n=32) and hybrid (n=15) PVR outcomes (procedural, mid-term, heart remodeling/function, arrhythmia,

symptom, functional, and HRQOL as well as cost outcomes) (Manuscript III). The results were compared to the surgical literature and TC and surgical meta-analysis outcomes.

Findings: Gaps identified in the quasi-meta-analysis (Manuscript I) were that hybrid PVR outcomes were limited to procedural outcomes. There were limited symptom and HRQOL outcomes for both TC and hybrid PVR. There were few reports of diastolic heart function for either TC or surgical PVR. The study (Manuscript III) showed hybrid PVR had similar heart remodeling outcomes as TC. There were no changes in heart function, arrhythmias, or exercise capacity for TC or hybrid PVR; this was similar to surgical PVR outcomes. Dyspnea and exercise intolerance decreased. Functional class improved but was only significant in the TC group which compares to surgical PVR. Length of stay was significantly shorter for TC and hybrid PVR than surgical PVR but costs were higher. Manuscript II demonstrated that the Omaha System was useful in aligning nursing theory and terminology to identify patterns between psychosocial characteristics and leg ulcers that could be investigated further. These skills in extracting and categorizing variables were used in designing the study reported in Manuscript II.

Conclusions: The findings from Manuscripts I and III should help health care providers to begin to educate patients/families about the best PVR treatment options given individual patient anatomy, physiology, and preferences. Manuscript II demonstrated that the Omaha System was useful with large datasets to link theory and data to identify potential new hypotheses to test. This theory could be used to identify possible hypotheses to test with congenital heart disease databases.

Key Words: pulmonary valve replacement, congenital heart disease, tetralogy of Fallot, nursing theory, Omaha system

Introduction

Background and Problem Statement

Congenital heart disease (CHD) is the most common birth defect in the United States affecting nearly 1% of births.(2) Currently 2.4 million individuals live with CHD in the United States. (1) Tetralogy of Fallot is the most common cyanotic defect (2, 3) accounting for about 5% of CHD. (4) Pulmonic stenosis accounts for an additional 5% of CHD.(3) Tetralogy of Fallot requires surgical intervention during childhood and pulmonic stenosis often requires either interventional or surgical treatment. After initial treatment the pulmonary valve can become regurgitant or stenotic. The treatment of pulmonary valve regurgitation with symptoms or right ventricular dilation requires pulmonary valve replacement (PVR). Severe pulmonary stenosis with symptoms or excessively high valve gradients may also require PVR.

Currently the gold standard treatment is surgical PVR. Less invasive methods of PVR have emerged with transcatheter (TC) PVR, developed in 2000.(5) TC PVR consists of placement of a pulmonary valve via a transvenous route with only a venous puncture wound. Hybrid (a combination of TC and surgical methods) PVR has been developed more recently for use when the right ventricular outflow tract is not circular in shape, too large for a TC valve, or when it is too difficult to place a valve via a transvenous approach. Various forms of hybrid PVR have been developed ranging from perventricular PVR(6) to pulmonary artery annular remodeling (7), pulmonary artery

plication via sternotomy to place a TC valve or use of an injectable pulmonary valve via sternotomy or mini-thoracotomy (8-10) with or without pulmonary artery plication.(11)

To investigate problems in CHD it is generally necessary to conduct multi-site studies to accrue a sufficient sample size of patients to determine clinical and statistical significance. Therefore, skills and methods are needed to handle large data sets of medical information including extraction and categorization of variables. As well, there is a vast amount of data into electronic health records that could be potentially mined to examine relationships among variables across large numbers of CHD patients.

Gaps in Knowledge

Health care providers can be confused by the three types of PVR and not be clear about their indications and potential outcomes which leads to difficulty in educating patients and families about the best procedure for their individual anatomy, physiology, risk factors, and preferences. As a nurse practitioner working in the field of congenital heart disease I was tasked with educating patients/families about the various PVR options and I did not feel I had enough information to adequately address questions. As a result, I undertook a quasi-meta-analysis of the PVR literature to determine outcomes to date of TC, hybrid, and surgical PVR (Manuscript I in the dissertation).

Due to the fact that multi-site studies with large databases are often necessary in CHD to accrue enough patients, I needed to develop my skills in handling large data sets and learn to “mine” information from these data sets to reveal new knowledge and answer nursing research questions. This led me to do further exploratory work in this

area in collaboration with researchers at the University of Minnesota (Manuscript II in the dissertation). The purpose of this manuscript was to determine how the Omaha System, a standardized terminology and model that enables terminology-theory testing in nursing research, could be used to identify novel patterns and risk factors. Due to the limited PVR data available, a large research dataset to investigate wound development was chosen for this analysis. I gained methodological experience classifying these data and applied an analytic approach, distinct from that used for clinical trials, to describe the data. This provided additional experiential training in secondary data analysis for future application with large cardiovascular data sets.

Gaps in the literature identified from the meta-analysis (Manuscript I) then lead to a secondary data analysis study of existing medical data at Cedars-Sinai Medical Center in Los Angeles comparing TC and hybrid PVR outcomes as well as comparisons of these outcomes to those reported in the surgical literature as well as the existing TC and hybrid literature (Manuscript III).

Theoretical Frameworks

The Wilson and Cleary conceptual model of health-related quality of life (12) was used in Manuscripts I and III. It specifies that biological and physiological variables impact symptom status which then influences functional status and general health perceptions. Characteristics of the individual such as personality, motivation, values, and preferences as well as characteristics of the environment such as psychological, social, and economic support can also affect symptom status, functional status, and general health perceptions. General health perceptions lead to overall quality of life which is also

influenced by non-medical factors. In patients with pulmonary regurgitation and pulmonary stenosis, the biological and physiological variables consist of the CHD, the surgical/interventional procedures they have undergone, arrhythmias, co-existing genetic syndromes which are common in tetralogy of Fallot and pulmonary stenosis (13) , and procedural variables. These variables impact heart function which then influences symptoms. Symptoms in turn limit functional status such as exercise capacity while symptoms and functional status impact HRQOL. Individual and environmental characteristics can impact symptoms, functional status, and HRQOL perceptions. A key question was whether PVR improves any of these outcomes. Therefore, when selecting variables to study, variables such as demographic characteristics, genetic syndromes, previous surgical details, procedural details, heart remodeling and function, arrhythmias, symptoms, functional status, and HRQOL were selected based on the Wilson and Cleary model. Few individual and none of the environmental characteristics such as social, psychological, and economic support could be incorporated into the study due to the limited sample size and limited data on these variables.

In Manuscript II, the Omaha System (14) was used which is a framework that classifies nursing problems, interventions, and nursing actions based on taxonomy. The Problem Classification Scheme consists of problems arranged into the domains of environment, psychosocial, physiological, and health-related behaviors. The Intervention Scheme addresses problems by category (e.g. teaching), target (e.g. medication administration), and care description. The Problem Rating Scale for Outcomes transforms the identified problems using 5-point Likert rating scales. Thus, the Problem

Rating Scales normalizes measurement across all health-related concepts. Data were extracted from a closed clinical trial that compared a cooling intervention to a placebo on ulcer prevention in a sample of patients with venous disease. The goal was to uncover new relationships amongst the variables that could be predictors of venous ulcers. The new variable relationships were then tested to determine model fit.

Design and Methods

To investigate patient outcomes after PVR a quasi-meta-analysis was performed of 85 surgical and 47 TC PVR studies published between 1995-2016 (Manuscript I). This manuscript merged integrative review findings on mortality, symptoms, functional status, HRQOL, and infective endocarditis after PVR using meta-analysis of the paired pre- and post-PVR quantitative measures using Comprehensive Meta-Analysis Version 3 (Biostat, Englewood, NJ). Variables examined were biological variables including cardiac MRI/MRA values of heart remodeling and function, arrhythmias, symptoms, functional status, and health-related quality of life (HRQOL). Meta-analyzed variables included right and left ventricular end-diastolic and end-systolic volume indices, ejection fraction, pulmonary valve regurgitant fraction, QRS duration, and peak oxygen consumption. Pooled pre- and post-PVR values were determined for each of the meta-analyzed variables as was a forest plot to determine the effect of TC and surgical PVR on the variables. Funnel plots were examined for each variable to determine study heterogeneity. There were insufficient hybrid PVR studies for meta-analysis. Gaps identified in the quasi-meta-analysis included the lack of post-procedural outcomes in hybrid PVR, a lack of paired pre- and post-PVR measures, very little HRQOL for TC

PVR, a lack of standardized definitions for complications vis-à-vis other TC valve literature and surgical literature, and a lack of outcome measures such as cardiac MRI/MRA reported at least one year post-PVR.

In Manuscript II demographic and outcomes data from an existing clinical trial database were transformed using Omaha System Problem Rating Scale for Outcomes to derive a theoretical framework. The variables were then examined using visualization techniques such as heat maps to generate hypotheses and predictive models for leg ulcers. Multivariate statistics were then used to evaluate model fit. The skills learned from this project informed the data extraction and variable classification process for the data set used for Manuscript III.

The gaps identified in the quasi-meta-analysis then lead to an exploratory study of TC (n=32) and hybrid (n=15) PVR outcomes from data extracted from the electronic medical records at Cedars-Sinai Medical Center in Los Angeles, CA covering the period from 2012 to early 2017 (Manuscript III). Variables were selected using the Wilson and Cleary conceptual model of HRQOL.(12). Pre- and post-PVR demographic and clinical characteristics were descriptively analyzed. Differences in pre- and post-PVR cardiac MRI/MRA, echocardiographic, electrocardiographic, arrhythmia (Holter monitor and Zio patch [iRhythm Technologies, San Francisco, CA]) symptom, NYHA Functional Class, cardiopulmonary exercise test, and PedsQL Core Scales and Cardiac Module for HRQOL. (15-17) HRQOL data were analyzed with paired t-tests or Wilcoxon signed rank tests for continuous outcomes or McNemar tests for proportional data. The results

from this study were compared to TC, hybrid, and surgical PVR outcomes from the literature.

Description of Manuscripts I, II, and III

Three manuscripts are presented in this dissertation. The first manuscript presents the quasi-meta-analysis of PVR outcomes from the literature. The second manuscript explores the application of the Omaha model to a large venous ulcer data set in order to use theory to generate hypotheses between variables in the data set and test those hypotheses. It also enhanced my large data set skills. The final manuscript presents a single-center exploratory study of TC and hybrid PVR outcomes.

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MANUSCRIPT I

McRae, ME, Coleman, B, Atz, TW, Kelechi, TJ. Patient Outcomes after Transcatheter and Surgical Pulmonary Valve Replacement for Pulmonary Regurgitation in Patients with Repaired Tetralogy of Fallot: A Quasi-Meta-Analysis. Eur J Cardiovasc Nurs. 2017 Aug; 16(6):539-553.

Online supplementary material (Figures 1-3, Table 1-2) are included at the end of manuscript.

Original Article

European Journal of Cardiovascular Nursing

ESC European Society of Cardiology

European Journal of Cardiovascular Nursing
2017, Vol. 16(6) 539–553

DOI: 10.1177/1474515117696384
journals.sagepub.com/home/cnu
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Patient outcomes after transcatheter and surgical pulmonary valve replacement for pulmonary regurgitation in patients with repaired tetralogy of Fallot: A quasi-meta-analysis

Marion E McRae[1,2,3], Bernice Coleman[4], Teresa W Atz[5] and Teresa J Kelechi[6]

Abstract

Background: Individuals with repaired tetralogy of Fallot develop pulmonary regurgitation that may cause symptoms (dyspnea, chest pain, palpitations, fatigue, presyncope, and syncope), impair functional capacity, and may affect health-related quality of life. Surgical pulmonary valve replacement is the gold standard of treatment although transcatheter pulmonary valve replacement is becoming more common. Patients want to know whether less invasive options are as good.

Aims: This analysis aimed to examine the differences in surgical versus transcatheter pulmonary valve replacement effects in terms of physiological/biological variables, symptoms, functional status and health-related quality of life.

Methods: This quasi-meta-analysis included 85 surgical and 47 transcatheter pulmonary valve replacement studies published between 1995–2016.

Results: In terms of physiological/biological variables, both surgical and transcatheter pulmonary valve replacement improved pulmonary regurgitation and systolic and diastolic right ventricular volume indices but not heart function. In the left heart, only surgical pulmonary valve replacement improved heart function. Only transcatheter pulmonary valve replacement improved left ventricular end-diastolic indices and neither improved endsystolic indices. Only surgery has been demonstrated to decrease QRS duration but there is little evidence of arrhythmia reduction. Symptom change is poorly documented. Functional class improves but exercise capacity generally does not. Some aspects of health-related quality of life improve with surgery and in one small transcatheter pulmonary valve replacement study.

Conclusion: Transcatheter and surgical pulmonary valve replacement compare favorably for heart remodeling. Exercise capacity does not change with either technique. Health-related quality of life improves after surgical pulmonary valve replacement. There are numerous gaps in documentation of changes in arrhythmias and symptoms.

Keywords

Pulmonary valve replacement, transcatheter pulmonary valve replacement, pulmonary regurgitation, tetralogy of Fallot, congenital heart disease

Date received: 19 August 2016; revised: 7 February 2017; accepted: 7 February 2017

[1]Medical University of South Carolina, USA
[2]Guerin Family Congenital Heart Program, Cedars-Sinai Medical Center, USA
[3]David Geffen School of Medicine, University of California at Los Angeles
[4]Nursing Research Department, Cedars-Sinai Medical Center, USA
[5]College of Medicine, Medical University of South Carolina, USA
[6]College of Nursing, Medical University of South Carolina, USA

Corresponding author:
Marion E McRae, Guerin Family Congenital Heart Program, Cedars-Sinai Medical Center, 127 South San Vicente Boulevard, AHSP A3404, Los Angeles, CA 90048, USA.
Email: memcrae1@gmail.com

Introduction

Congenital heart disease (CHD) is the most common birth defect in the USA affecting nearly 1% of births.[1] Tetralogy of Fallot (TOF) is the most common cyanotic CHD (5.4% of CHD)[2] and has four features: (a) a membranous ventricular septal defect; (b) an over-riding aorta; (c) right ventricular outflow tract obstruction; and (d) right ventricular hypertrophy. Successful surgical repair of TOF has been performed since 1955.[3] Thirty-year survival is currently 80–90%.[4–7] Repair of TOF leaves pulmonary regurgitation (PR) that is well tolerated for years, but about 36–40%[8,9] of adolescents and adults with repaired TOF will need a pulmonary valve replacement (PVR) within 30 years of their initial childhood surgery. PVR has become the most common cardiac operation performed in adults with CHD.[10]

The problems that occur with PR in repaired TOF are well suited to the use of Wilson and Cleary's conceptual model of health-related quality of life (HRQOL)[11] (see Supplementary Material, Figure 1). In PR after TOF repair, the primary problems are the biological/physiological variables, with PR initiating many of the other sequelae (see Supplementary Material, Figure 2), leading to ventricular arrhythmias (14.6%),[12] sustained atrial tachyarrhythmias (20.1%),[12] right ventricular (RV) failure,[13] and ultimately left ventricular (LV) failure.[13] About 40% of individuals with repaired TOF will die of heart failure and about 10% will suffer sudden death, likely arrhythmic in origin.[14] The deleterious effects of PR and heart failure in repaired TOF have been identified as top priority research priorities in adult CHD.[15,16]

As a result of the biological/physiological variables, symptoms such as dyspnea on exertion, fatigue, palpitations, chest pain, presyncope, and syncope occur affecting about 45% of TOF patients.[4] Symptoms impair functional status[4] including exercise capacity and this can impair general health perceptions such as HRQOL. HRQOL has an impact on overall quality of life that is also influenced by nonmedical factors.

Currently, surgical PVR is considered the gold standard of treatment for PR but is very invasive requiring a sternotomy, the use of cardiopulmonary bypass, and weeks of recovery. The biologic valves used eventually deteriorate and require replacement. Although mechanical valve PVR can be used, concern about the effects in the low-pressure pulmonary circulation with the requirement for anticoagulation in active individuals has limited its use. Mechanical PVR will not be considered in this review. The reader is referred to a meta-analysis on this topic.[17]

Transcatheter (TC) PVR approaches have been developed for TOF with a right ventricle to pulmonary artery conduit.[18,19] More recently PVR approaches with native outflow tracts (without conduits) have been developed including hybrid (combination of TC and surgical techniques) to address the problem of outflow tracts that are larger than the available valves. These approaches vary in their invasiveness from a small 5–10 cm incision[20,21] to full sternotomy[22–25] and some approaches use cardiopulmonary bypass.[21] When the surgical or TC valve deteriorates, replacement via TC PVR techniques can be done (valve-in-valve PVR).[26–30] Although most patients prefer less invasive approaches to PVR they have questions for healthcare professionals about how they compare with surgical PVR. There are no known comparisons of the TC, hybrid, and surgical PVR at this time making it difficult for providers to advise patients.

Therefore, this review sought to address whether there are differences between TC and hybrid PVR versus surgical PVR on biological variables (heart remodeling and function, arrhythmias), symptoms, functional status, and HRQOL in patients with PR after TOF repair. This review did not address the literature on valve longevity.

Methods

This review was undertaken using a quasi-meta-analysis technique (integrative review with meta-analysis of the quantitative variables). The Meta-Analyses of Observational Studies in Epidemiology[31] criteria were used in reporting the results. A medical librarian was consulted for search design (see Supplementary Material, Table 1). The inclusion and exclusion criteria are shown in Supplementary Material, Table 1.

The search process is shown in Supplementary Material, Figure 3. The Wilson and Cleary[11] framework guided variable extraction and reporting. All outcome measures were extracted into Excel spreadsheets for comparison. For multiple point outcomes in a study, the outcomes with the longest follow-up time were used provided the number of observations was not extremely small. Where studies reported subgroups of patients, only those with PR were used. Data from magnetic resonance imaging (MRI), EKG, and cardiopulmonary exercise tests were analyzed using Comprehensive Meta-Analysis Version 3 (Biostat, Englewood, New Jersey, USA) where possible to assess combined effect size from multiple measures. This analysis depended on pre- and post-PVR measures, and p values for each study. Studies found to have incorrect p values based on the means were excluded. Studies not using pre- and post-testing were excluded from the quantitative analysis but were included in the qualitative synthesis. The level of significance was set at $p<0.05$. A random effects model was used for testing due to study heterogeneity.[32] Although the first author performed the search and data extraction, all authors guided the analysis was to ensure robust conclusions.

Results

General characteristics of the studies are described first followed by patient outcomes organized according to the Wilson and Cleary model.[11]

Study characteristics

A total of 47 TC PVR manuscripts were reviewed (37 with primarily conduit implants and 10 with primarily native RV outflow tract implants with 3354 subjects). These were compared and contrasted with outcomes from the gold standard surgical PVR (85 manuscripts) with 6196 subjects (see Supplementary Material, Table 2). There were insufficient hybrid studies (four) and therefore an analysis of hybrid PVR was not undertaken. Studies involving exclusively valve-in-valve implants were excluded. Many of the studies were conducted with heterogeneous samples (patients with different diagnoses and past surgeries; few studies were conducted solely with patients with repaired TOF with primary PR) but only those reporting TOF patients as the largest subgroup were included. Study participants ranged in age from older children to middle-aged adults.

The sample sites were, in descending order, the USA, the Netherlands, Canada, Belgium, the UK, France, Korea, Germany, France, and single studies from other European and Asian countries. Sites were large pediatric and/or adult academic teaching hospitals. Sample sizes varied from 5–404 subjects. There were 16 single-center and 31 multisite TC PVR studies whereas most of the surgical studies were single-center studies. There may be some subject overlap between studies, particularly in ongoing trials but this was difficult to ascertain.

The TC study designs were a mix of retrospective and prospective cohort designs (sometimes difficult to determine) versus predominantly retrospective cohorts in surgical PVR. There were a few matched cohort studies, all but one in the surgical group. There was one randomized study comparing surgical PVR with and without RV remodeling procedures.[33] In contrast to the surgical PVR literature dating back several decades, the first TC study cited was in 2006.

Patient outcomes

Biological and physiologic variables. Assessment of right and left heart volumes, regurgitant fraction (RF) of the pulmonary valve, and heart function (ejection fraction) with cardiac MRI/magnetic resonance angiography (MRA) was performed to determine if the heart remodels and ventricular function normalizes after PVR. Some studies used paired results and others did not therefore only studies with paired results were used in the meta-analyses. Cardiac MRI/MRA was performed in 31 surgical studies and 15 TC studies from a median of six months to 3.5 years and 1–2 days to 16 months post-operatively (most at six months) respectively.

Heart volume indices. RV end-diastolic index (RVEDVI) significantly decreased from a pooled pre-PVR value of 129.77 to 106.07 ml/m^2 after TC PVR (p<0.001) and from a pooled pre-PVR value of 173.96 to 112.26 ml/m^2 after surgical PVR (p<0.001). RV end-systolic volume index (RVESVI) was significantly reduced from a pooled value of 68.00 to 56.71 ml/m^2 after TC PVR (p<0.001) and from 100.13 to 60.84 ml/m^2 (p<0.001) after surgical PVR. Pulmonary valve RF decreased significantly from a pooled value of 32.56% to 3.55% after TC PVR (p<0. 001) and from 45.77% to 6.37% (p<0.001) after surgical PVR (see Figures 1 and 2 for right heart forest plots). LV end-diastolic index (LVEDVI) was significantly increased after TC PVR from a pooled value of 78.53 ml/m^2 to 85.71 ml/m^2 (p<0.001), likely due to improved filling of the left ventricle. There was no significant change in surgical LVEDVI (pooled pre-PVR values of 33.05 to 34.44 ml/m^2 post-PVR, p=0.929). LV end-systolic volume index (LVESVI) did not change after TC (pre-PVR pooled value of 43.63 ml/m^2, post-PVR 46.25 ml/m^2, p=0.067) or surgical PVR (pre-PVR pooled value of 33.05 ml/m^2, post-PVR pooled value of 34.44 ml/m^2, p=0.252), see Figures 3 and 4 for the left heart forest plots.

Systolic function. Systolic right heart function improvement was not evident after PVR. The RV ejection fraction (RVEF) did not change after TC (pre-PVR pooled value of 45.82%, post-PVR pooled value of 47.19%, p=0.631) and surgical PVR (pre-PVR pooled value of 44.67%, post-PVR pooled value of 44.81%, p=0.282). The LV ejection fraction (LVEF) did not significantly increase after TC PVR (pre-PVR pooled value of 58.4%, post-PVR pooled value of 58.35%, p=0.140) but it did after surgical PVR (pre-PVR pooled value of 55.94%, post-PVR pooled value of 58.07%, p<0.001), indicating improved left heart systolic function with surgery.

Arrhythmias. QRS duration on the 12-lead EKG (electrocardiogram) was significantly reduced after surgical PVR (pre-PVR pooled value of 156 ms to 150 ms, p<0.001) but not after TC PVR (pre-PVR pooled value of 142 ms both before and after PVR, p=0.729). There were only two studies (both at six months post-procedure) in the TC group (one study without enough information for meta-analysis not included). Surgical QRS duration was measured in 28 studies (19 with analyzable data) from less than one month to nine years post-operatively. See Figure 5 for QRS duration forest plots. Some studies reported a reduction in arrhythmias with PVR[34] but the results were inconsistent.[35–37] With the variety of concomitant procedures for arrhythmias undertaken with surgical PVR (cryoablation, right atrial and bi-atrial MAZE procedures, ablation of ventricular tachycardia) it was difficult to ascertain what effect PVR has on arrhythmia status.

Procedural morbidity and mortality. The surgical PVR studies reported a 30-day mortality of 1% (range 0–10% in 41 studies). In contrast, although there is 0.3% mortality (range 0–1.6% in 18 studies) after TC PVR there can be procedural failure as it is impossible to accurately assess for aortic (incidence 9.2%) and coronary artery

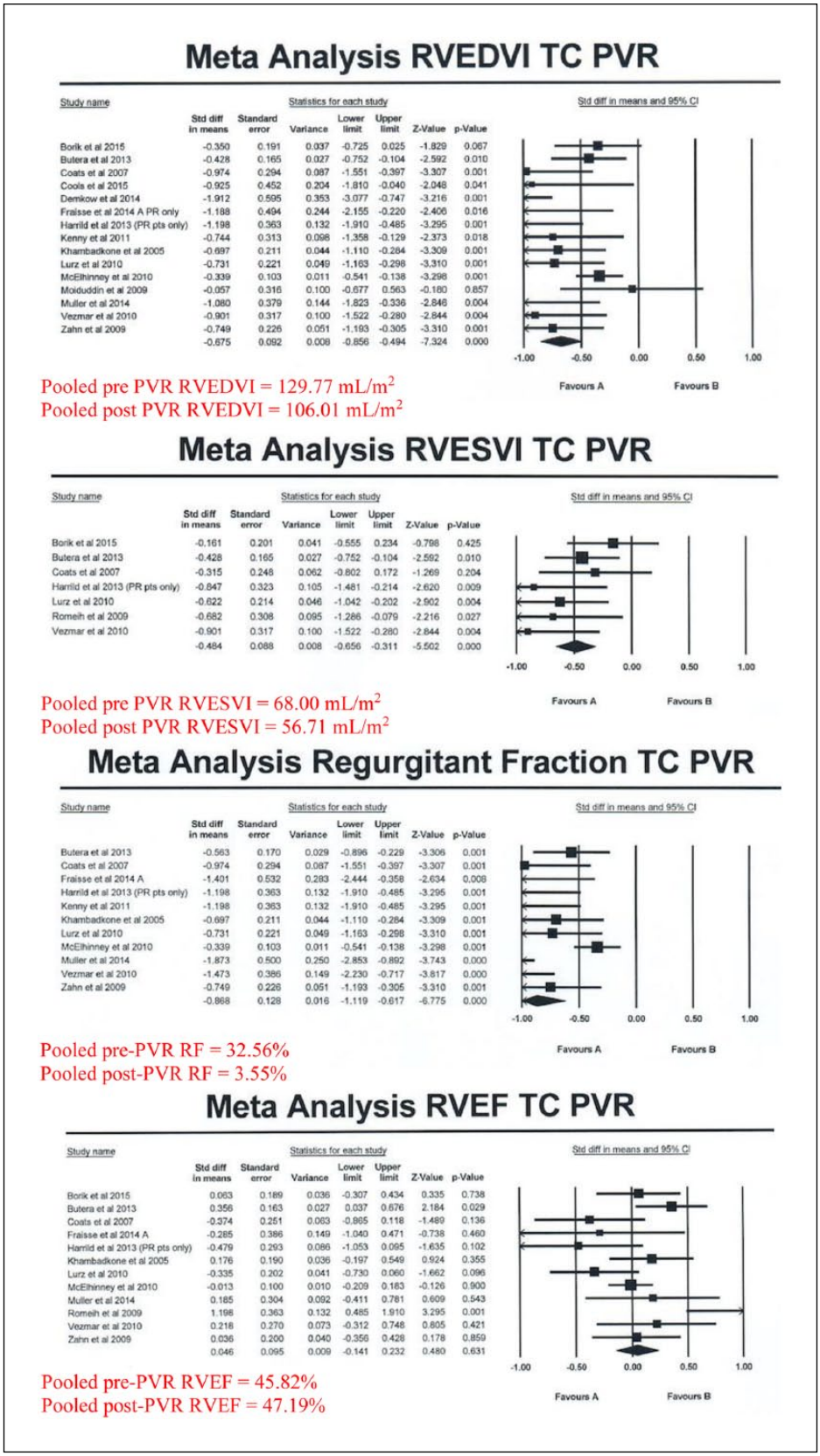

Figure 1. Forest plots of right heart transcatheter (TC) pulmonary valve replacement (PVR) outcomes. RF: regurgitant fraction; RVEDVI: Right ventricular end-diastolic index; RVEF: right ventricular ejection fraction; RVESVI: right ventricular end-systolic volume index.

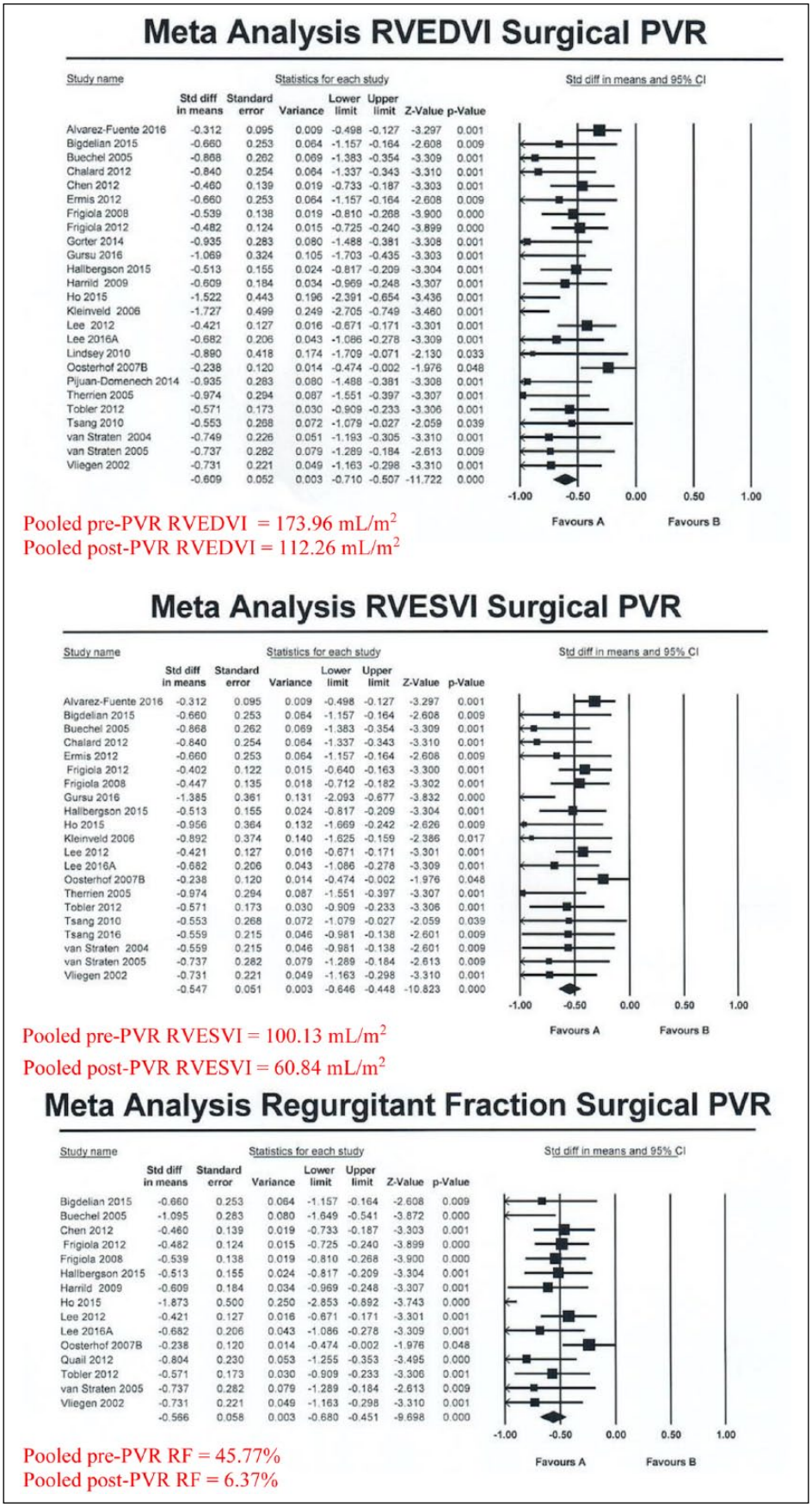

Figure 2. (Continued)

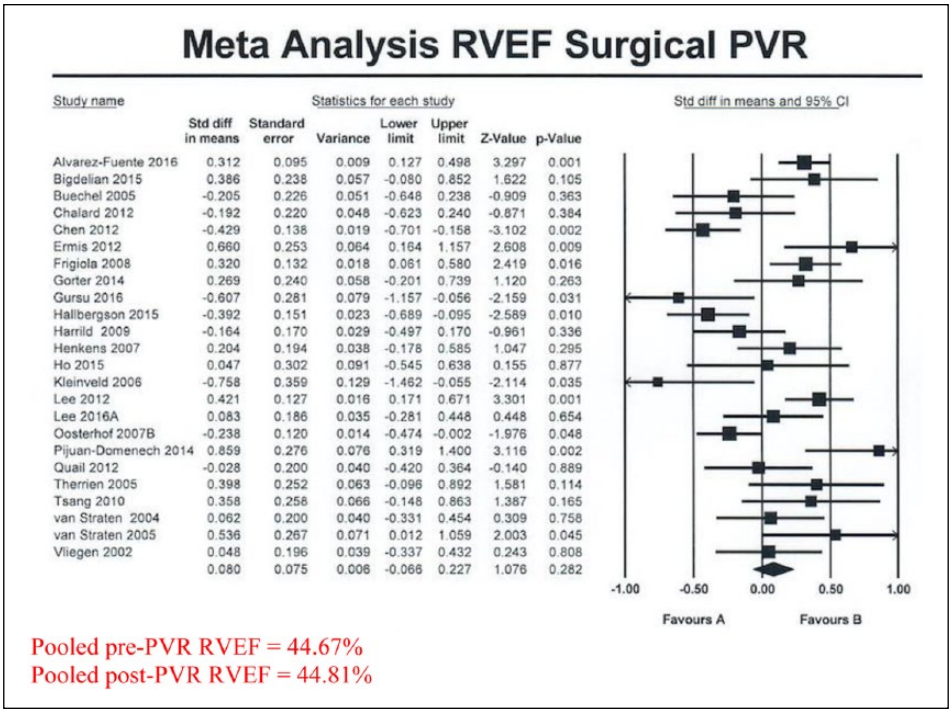

Figure 2. Forest plots of right heart surgical pulmonary valve replacement (PVR) outcomes. RF: regurgitant fraction; RVEDVI: Right ventricular end-diastolic index; RVEF: right ventricular ejection fraction RVESVI: right ventricular end-systolic volume index.

compression (incidence 4%) without balloon testing at implantation.[38] This does not occur with surgical PVR. In addition, stent or valve embolization is possible (incidence of 0.5–4.2% in studies reporting this complication)[30, 39-44] but many studies had none. Unlike surgical valves, the Melody TC valve has problems with stent fracture (34 studies with an incidence of 0–33.3% in this review). As fractures can impair valve function, pre-stenting has now become common (the stented valve is delivered into at least one stent placed in the right ventricle outflow tract) with a reduction in stent fracture. The Sapien TC valve has few reports of stent fracture due to the stronger stent metal. The surgical literature reports 5- and 10-year survival of 92%[45] to 98%[46] and 76.4%[47] to 100%[48] after PVR respectively. There is insufficient long-term follow-up to provide this data for TC PVR. Hospital stay was a median of 6.5 days and two days respectively for the surgical and TC studies.

Symptoms. One would expect symptoms to improve if the heart remodels after PVR. None of the TC studies evaluated the percentage of patients with specific symptoms such as dyspnea on exertion, fatigue, palpitations, chest pain, pre-syncope, and syncope before and after PVR. Two studies[48,49] evaluated symptoms in surgical PVR patients but no statistical significance testing was used. It was often unclear at what time point the symptoms were re-evaluated post-PVR. Some studies used the New York Heart Association (NYHA) functional class as a surrogate for symptoms.

Functional status. The most common indicator of functional status examined was the NYHA functional class. After TC and surgical PVR, NYHA functional class decreased significantly in all studies, but the multiple reporting methods made statistical comparison difficult. Many studies presented illustrations of NYHA functional class decrease but absolute numbers or percentages were lacking. Cardiopulmonary exercise testing was used in a smaller number of studies (12 TC, nine surgical) to examine exercise capacity at less than one month to 3.4 years post-PVR (most TC studies were at one year or less). Not all studies were maximal (interpretable). Peak oxygen consumption (VO_2 max) did not significantly increase after surgical PVR (pre-PVR pooled value of 26.75 ml/kg/min, post-PVR 27.15 ml/kg/min, p=0.885) but it did improve after TC PVR (pre-PVR pooled value of 31.69 ml/kg/min to 34.76 ml/kg/min, p=0.005). See Figure 6 for forest plots of VO_2 max. Very few studies reported other cardiopulmonary exercise variables.

General health perceptions (HRQOL). Five surgical studies[25,33,50–52] examined HRQOL using the 36-item short form survey (SF-36)[53] tool six months to four years post-operatively. One pediatric surgical study[33] used the Child Health Questionnaire[54]-Parent Form and another used a 10-item short form for children.[25] Significant improvement occurred in many of the SF-36 measures after surgical PVR indicating improved HRQOL. There

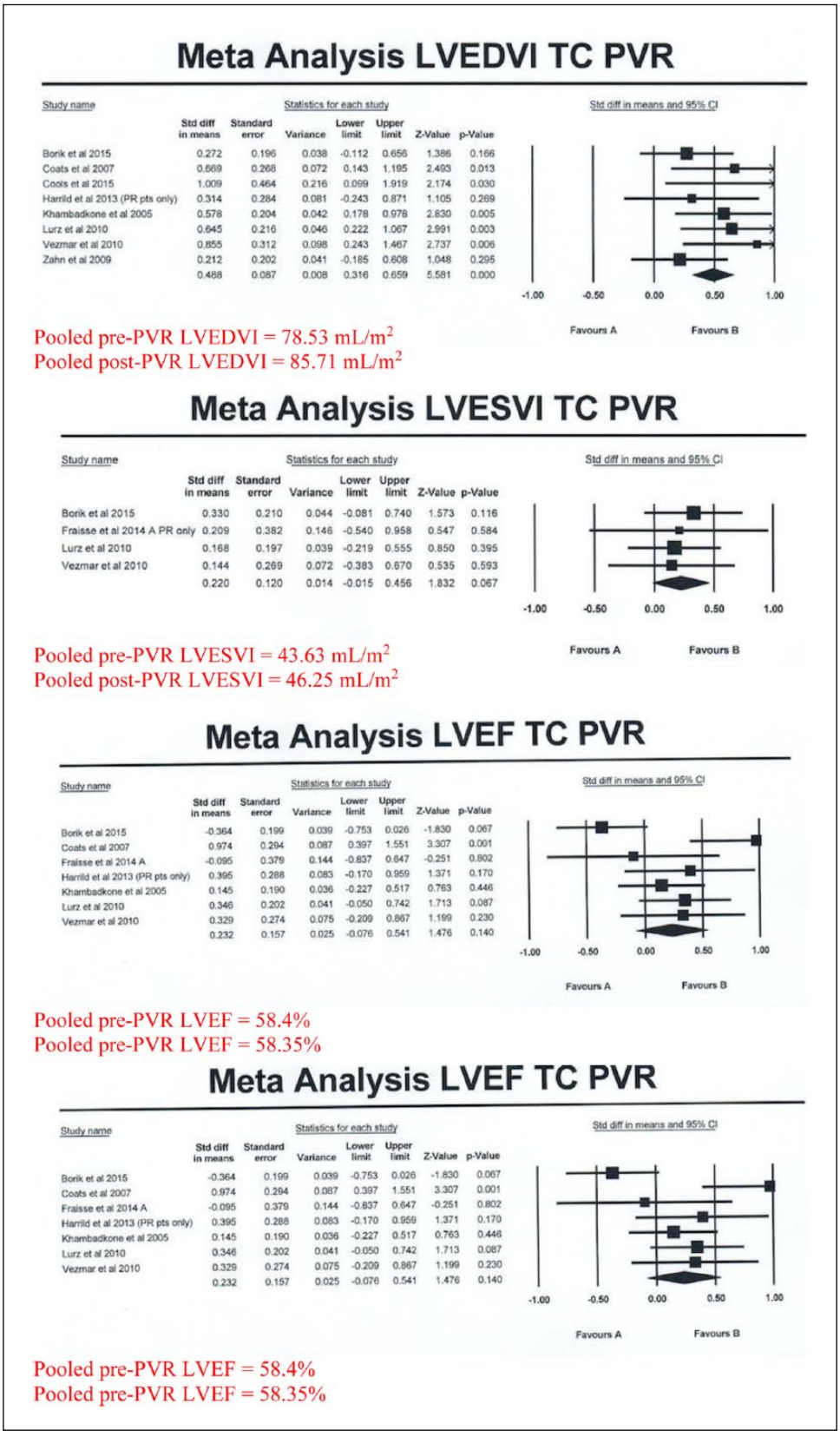

Figure 3. Forest plots of left heart transcatheter (TC) pulmonary valve replacement (PVR) outcomes. LVEDVI: left ventricular end-diastolic index; LVEF: left ventricular ejection fraction; LVESVI: left ventricular end-systolic volume index.

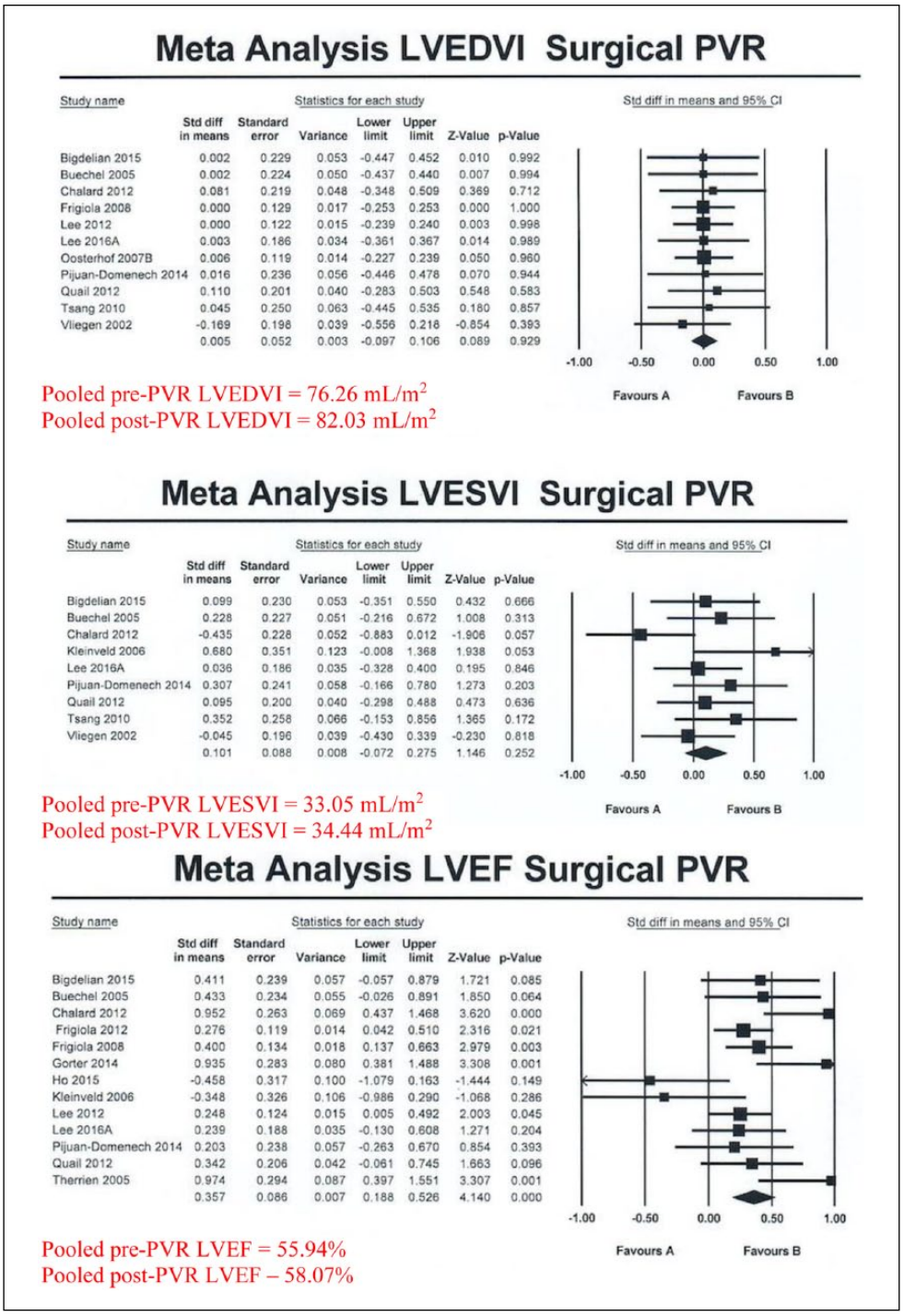

Figure 4. Forest plots of left heart surgical pulmonary valve replacement (PVR) outcomes. LVEDVI: left ventricular end-diastolic index; LVEF: left ventricular ejection fraction; LVESVI: left ventricular end-systolic volume index.

was only one study with 13 subjects examining HRQOL measured with the SF-36 instrument six months after TC PVR.[55] Only physical health scores and health transition scores significantly increased. Four of the subscales had perfect scores before PVR therefore making it impossible to assess any improvement.[55] No disease-specific HRQOL instruments were used. The studies lacked definitions for HRQOL and failed to distinguish this concept from overall quality of life.

Infective endocarditis

Although this study did not specifically examine infective endocarditis (IE) due to the problems of multiple

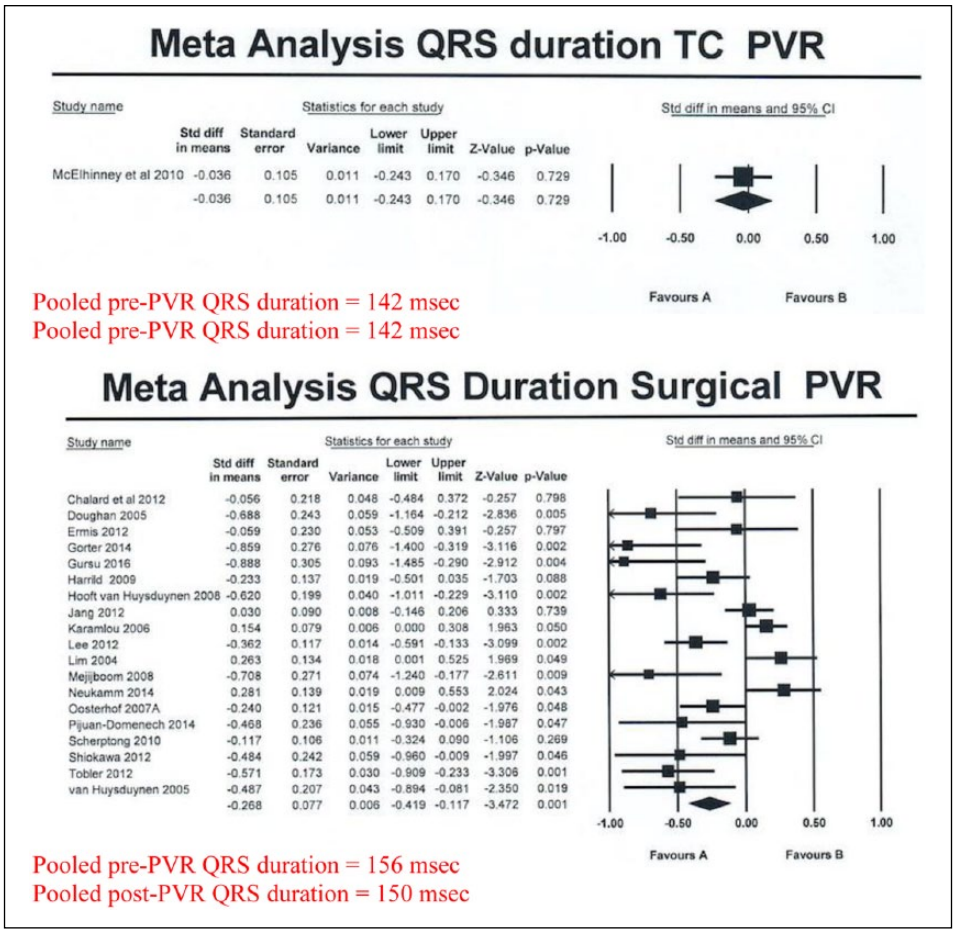

Figure 5. Forest plots of QRS duration pulmonary valve replacement (PVR) outcomes.

definitions in the literature and the lack of follow-up for IE in many of the surgical studies, a few important points should be made. A higher incidence of IE has been noted with the Melody bovine jugular valve with reports of 0.1–14.3%[44,56–67] and a 2.4% annulated rate of IE.[68] Higher rates of IE have been reported in surgical bovine jugular vein conduits versus homografts.[69] The reason for the high incidence of IE in bovine jugular conduits and valves is not clear at this time.

Discussion

Biological and physiologic variables

If one expects improvement of physiologic variables after PVR, assessment of the variables needs to be performed after adequate time for cardiac remodeling to occur. There was no consistent time frame for conducting MRIs after PVR. One of the studies reported MRI results performed only 1–2 days after PVR[70] and several other studies performed post-PVR MRIs within the first month,[44,71] a time frame likely providing insufficient time for ventricular remodeling. Most studies reported only single post-PVR MRI measures. Of the surgical PVR studies, there are three that report serial MRI data.[72–74] The RVEDVI, RVESVI, and RVEF showed a small improvement from 7–8 months post-PVR to 19–22 months post-PVR although the changes from eight months to 22 months were not statistically significant.[73,74] A third study[72] showed a small reduction in RVESVI, no change in RVEDVI, and a slight increase in RVEF (all non-significant from changes up to one year post-PVR) at 1–2 years. This was then followed by a slow increase in RVEDVI and RVESVI over the following years up to 10 years with a progressive increase in RF over time as well. LVEF and RVEF remained stable until after seven years when they started to decline.[72] A recent study[62] of unpaired volume indices for a mean of 4.5 years after TC PVR showed that there was no further remodeling of heart volume or function after one year. This should be confirmed by future studies that have paired MRI/MRA measures. Further studies with serial MRI assessments would be useful to confirm when remodeling is complete and if the right ventricle starts to dilate again. Serial MRI studies are also needed to understand how the heart responds to a second or third PVR, as this is what many repaired TOF patients will face over their lifetime.

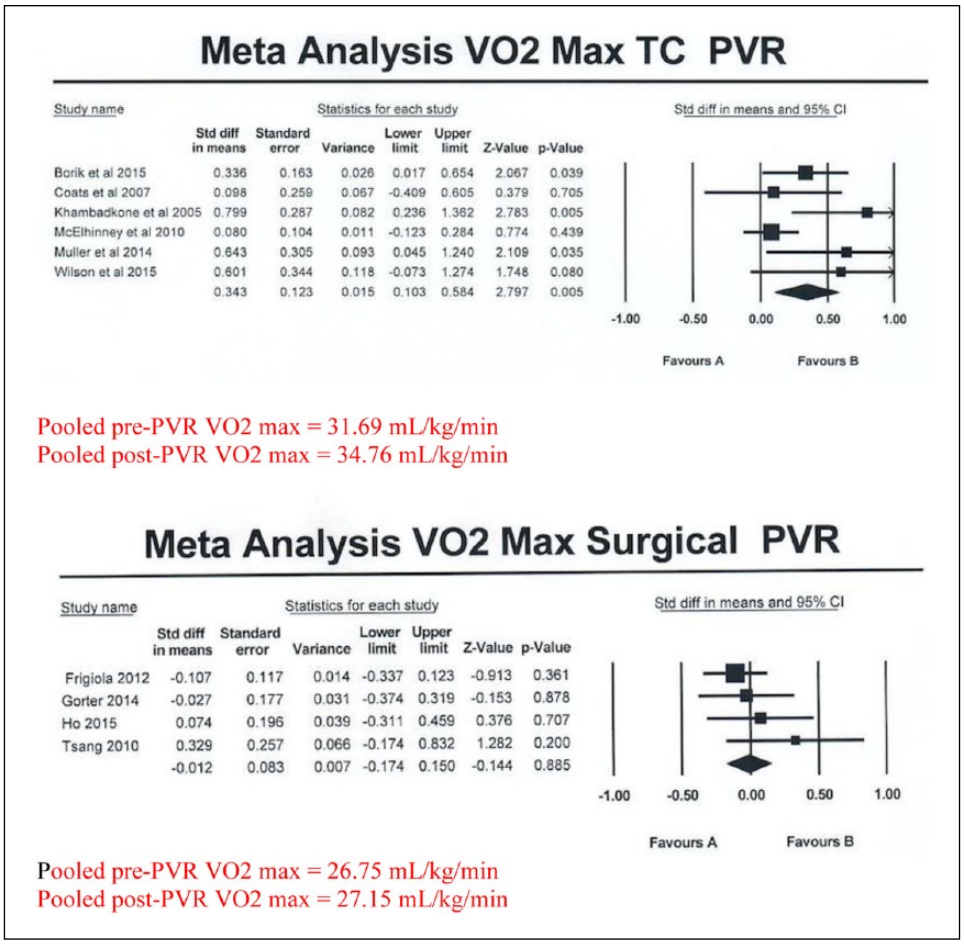

Figure 6. Forest plots of peak oxygen consumption (VO_2 max) pulmonary valve replacement (PVR) outcomes.

Heart volume indices. This study found that implanting a valve, either surgical or TC, improves PR immediately followed by significant reduction in size of the right ventricle in diastole due to the resolution of PR. In TC PVR, the LVEDVI increased significantly but in surgical PVR there was no change. It is unclear if the surgical LVEDVI will not change or lags behind RV recovery as the effects on the left ventricle are indirect and also subject to surgical insults such as cardiopulmonary bypass. The fact that TC PVR was performed at smaller right ventricular volumes may also cause some of the differences.

Systolic function. Left heart systolic function significantly improved after surgical PVR, likely due to decompression of the dilated right ventricle and a shift of the interventricular septum back to a normal position. This results in improved filling of the left ventricle.[75] LVEF did not improve after TC PVR but this may be due to a higher LVEF before the PVR. Right ventricular systolic function did not change after surgical and TC PVR. It may be that further time is required for recovery of RV function. Some studies have found that recovery occurs in individuals with less dilated right ventricles but these results have been inconsistent.[33,76–81] Larger trials with serial follow-up are needed to determine if there is a threshold above which recovery will not occur. Some of the issues related to RV contractility may be measurement-related. Ferraz Cavalcanti and co-authors[82] found that surgical PVR studies using corrected measures of RVEF versus non-corrected measures demonstrated a significant increase in RVEF. However, measurement methods are not specified in some studies.

There may be other biologic factors that determine ventricular remodeling such as the duration of cyanosis before primary TOF repair. Genetic factors may impact outcomes of PVR given the high prevalence of genetic syndromes with TOF.[83,84] Age may play a role in ventricular remodeling as Borik and colleagues[62] showed that TC PVR at less than 16 years of age was associated with better ventricular remodeling.

Two studies reported MRI/MRA parameters after hybrid PVR but owing to incomplete data they could not be meta-analyzed and therefore comparisons were limited to TC PVR versus surgical PVR. In addition, there is considerable variability in the hybrid procedures that make comparisons difficult. Many of the hybrid PVR approaches

are supported by little more than feasibility data with short follow-up at this time.

Arrhythmias

This study found that surgical PVR significantly decreases QRS duration. Only two studies,[57,85] document QRS duration reduction in TC PVR (only one with sufficient data to be included in the meta-analysis). The differences may be due to the fact that the RV sizes were substantially larger in the surgical group versus the TC group. Smaller RV size promotes more rapid interventricular conduction. Arrhythmia reduction has not been well documented despite decreases in the QRS duration for surgical PVR. Few studies report anything other than qualitative summaries of arrhythmias. Many arrhythmias may be subclinical and only found on longer-term surveillance such as Zio patch (iRhythm Technologies, San Francisco, California, USA). Regular, longer-term arrhythmia surveillance would improve information on prevalence of arrhythmias. Definitions of arrhythmias would also be helpful as these were often lacking.

Symptoms

Patients often make decisions to undergo PVR due to symptoms. Although many TC patients anecdotally report subjective symptom relief, this has yet to be clearly documented for each symptom such as dyspnea on exertion, chest pain, palpitations, fatigue, presyncope, and syncope. Only two surgical PVR studies[48,49] described specific symptoms. Some studies used NYHA functional class as a surrogate for symptomatology but percentage of symptom change with PVR would help patients make decisions about whether or not to proceed with PVR.

Functional status

NYHA functional class was decreased after PVR suggestive of improvements in exercise capacity, but the measures varied widely (often pictorially without numbers) so a quantitative comparison was not performed. Some studies reported outcomes for all four functional classes; others grouped some categories together. Future studies should report absolute numbers and percentages of subjects in each NYHA class before and after PVR. It was unclear in many studies when the NYHA functional classification was performed after PVR.

NYHA is a subjective evaluation of functional status. In CHD functional decline often occurs slowly and patients underestimate their exercise capacity.[86] Therefore the American adult CHD guidelines recommend objective cardiopulmonary exercise testing.[87] VO_2 max, a measure of aerobic capacity, did not significantly change with surgical PVR but it did with TC PVR. However, there were a limited number of studies in both groups that could be included in the analysis so these results are preliminary. Also, VO_2 max was lower in the surgical PVR group pre-PVR and this may influence the results. Most of the cardiopulmonary exercise studies were performed about six months after PVR and further improvement may occur later in the course of recovery, especially if heart remodeling takes time. One study with unpaired exercise tests performed at a median of 0.53 and 3.4 years after TC PVR showed that although there were no significant changes in VO_2 max or work performed at the earlier measurement, both changed significantly at the later test.[62] Therefore serial post-PVR measures or measures at one year or beyond are recommended in future studies.

General health perceptions

Five studies examined HRQOL in surgical PVR and one study in TC PVR and all found some improvements as measured by a generic HRQOL instrument. Some pre-PVR ceiling effects were observed in subscale measures making it impossible to assess any improvement post-PVR. Several studies[88,89] have shown that the SF-36 may not have sufficient sensitivity in valve patients, particularly those who are young with few comorbidities. Disease-specific HRQOL measures alone or in combination with generic HRQOL measures may yield more information than generic tools alone. Instruments accommodating both pediatric and older age groups may be needed.

The strength of the association between symptomatology, functional status, and HRQOL before and various types of PVR should be investigated to understand which factors affect HRQOL the most and what treatment targets may benefit patients most. As well, other moderators of HRQOL such as the personal and environmental factors in the Wilson and Cleary model[11] need further study.

Gaps in the literature and implications for research

The lack of variable definitions created important heterogeneity in the reporting of outcomes amongst the studies. More precise definitions, or standardized definitions would facilitate cross-study comparison, pooling of results in meta-analyses, or in multi-site studies. Longer-term follow-up of TC PVR and hybrid PVR is needed to compare with the long-term surgical PVR outcomes. Outcome measures at least one year post-PVR and serial measures are needed to understand how the heart remodels and whether arrhythmias change over time after cardiac remodeling. As more experience is reported with TC valves, durability versus surgical valves will require further study.

Precision indicators and effect sizes should be reported in future studies to facilitate meta-analyses and estimate power for future studies. When sample sizes are small

pre- and post PVR paired measures would be useful, as significant differences can exist amongst subjects in small cohorts.

Only three TC studies were comprised solely of patients with TOF and none of the data were included in the meta-analyses. Of the surgical PVR studies, 53 included only patients with TOF and 31 contributed data to the meta-analyses. When the studies that were not completely patients with TOF were removed from the analyses, none of the meta-analyses outcomes changed. Future studies of TC PVR should address the TOF group separately.

Implications for practice

TC and surgical PVR compare favorably for short-term outcomes at this time. TCPVR had more increase in LVEDVI and exercise capacity (VO_2 max). Surgical PVR was superior for increase in LVEF. Surgical PVR had more decrease in QRS duration but there is no known difference in arrhythmias between the two techniques. No statement of comparability can be made for hybrid and valve-in-valve versus surgical PVR at this time due to the limited literature. The information gained from this review can be used to inform health care professionals about the outcomes of TC PVR versus surgical PVR. They may use this information to educate patients about the expected risks, benefits, and outcomes of these procedures so that they can make an informed decision about which type of PVR they prefer. The information in this review provides initial benchmarking data to use in TC PVR programs for quality improvement initiatives. The Wilson and Cleary framework[11] was useful in organizing a large number of variables examined in the studies. Support for many of the relationships depicted in the concept map of TOF (Supplementary Material, Figure 2) were demonstrated in the studies although further study is needed to specify causal relationships.

Limitations

Although this review has examined PVR outcomes from a large number of studies, it is influenced by the factors identified above and the fact that almost all studies were observational cohorts, many of them retrospective. There was only one randomized controlled trial, which limits causal generalization. The heterogeneity of TC PVR studies and the small numbers of studies of valve-in-valve PVR and hybrid PVR prevent separate analyses at this time. Some studies include small numbers of patients with pulmonary regurgitation after treatment for pulmonic stenosis patients or mixed pulmonary regurgitation and stenosis that were not analyzed separately from the pulmonary regurgitation patients. As well as this, not all studies were comprised totally of TOF patients (particularly in the TC PVR group). However, the results of the meta-analyses are not changed when studies with other CHD diagnoses are included. The influence of genetic factors on outcomes was not explored nor was valve durability, or stent fracture.

There are several methodological limitations of this review. A single author conducted the review which may have introduced bias reducing the validity or generalizability of the results. Important studies may have been excluded in the search. There were five abstracts in languages other than English and four conference abstracts that were irretrievable. These omissions may have influenced the results. There was publication bias evident from the funnel plots (not shown). As a result, negative or small studies may have underreported, introducing bias. A review of this size also limits reporting in detail on any of the variables examined.

Few studies[40,90] currently address indices of diastolic function despite the increasing recognition of the prevalence of both LV and RV diastolic dysfunction in repaired TOF (13.8% and 52.4% respectively in a multicenter cohort).[91] Diastolic dysfunction is a major determinant of exercise capacity[92] and an independent predictor of ventricular tachyarrhythmias[12] so further understanding of the diastolic dysfunction will be important.

Conclusions

TC PVR compares favorably with surgical PVR in terms of ventricular remodeling at this time but there is no improvement in arrhythmias with either PVR technique. Functional status may improve more with TC PVR but there are only a small number of studies to support this finding at present. Symptom improvement occurs but is poorly documented. Surgical PVR increases HRQOL but only one small study has investigated HRQOL in TC PVR. Longer follow-up of TC and hybrid PVR outcomes are needed.

Implications of pulmonary valve replacement for practice

- Transcatheter and surgical pulmonary valve replacement achieve partial ventricular remodeling
- There is little evidence of arrhythmia reduction
- Symptom reduction has not been well reported
- Some evidence of exercise improvement with transcatheter pulmonary valve replacement
- Only short-term outcomes of transcatheter and hybrid pulmonary valve replacement are reported

Conflict of interest

The authors declare that there is no conflict of interest.

Funding

This project received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. Marion E McRae

is supported by a Future of Nursing Scholar award from the Robert Wood Johnson Foundation, Princeton, New Jersey, USA and Cedars-Sinai Medical Center, Los Angeles, California, USA.

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Figure 1. The Wilson and Cleary conceptual model of health-related quality of life[11]

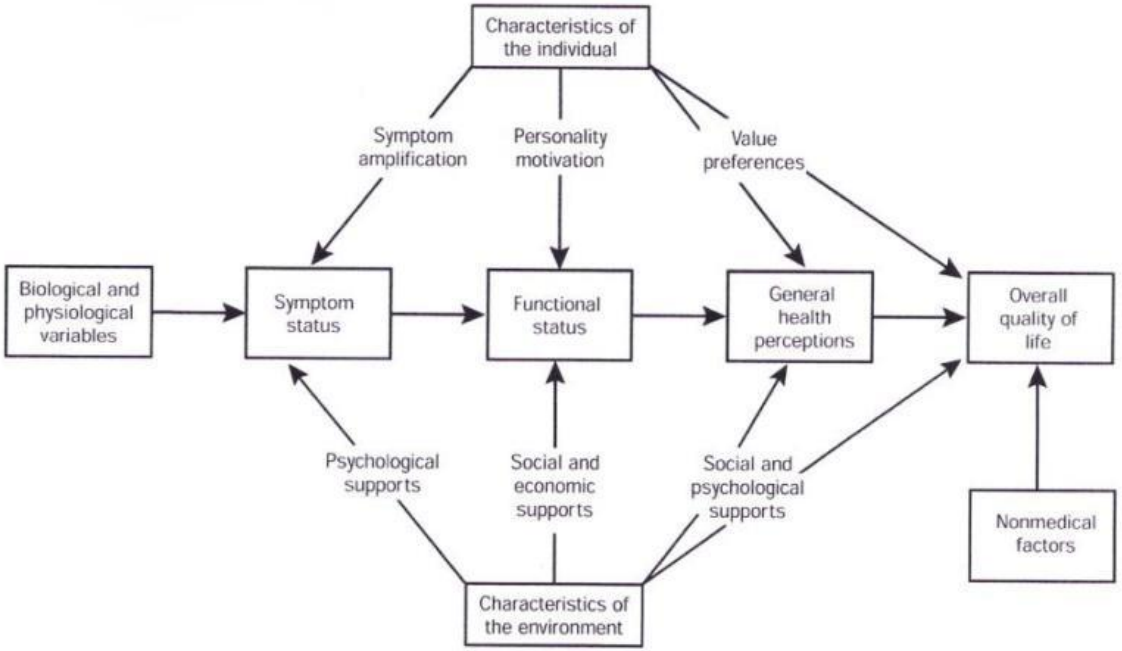

Figure 2. Concept map of tetralogy of Fallot

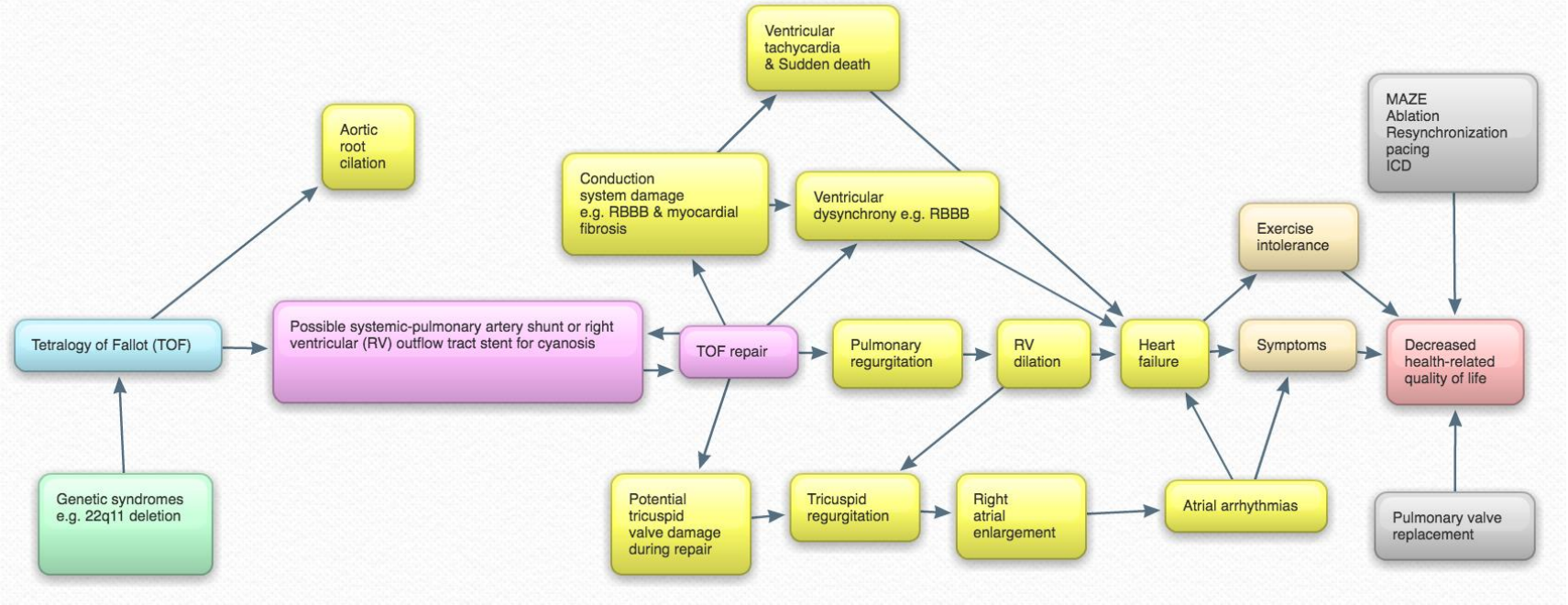

Figure 3. PRISMA Diagram of the search process

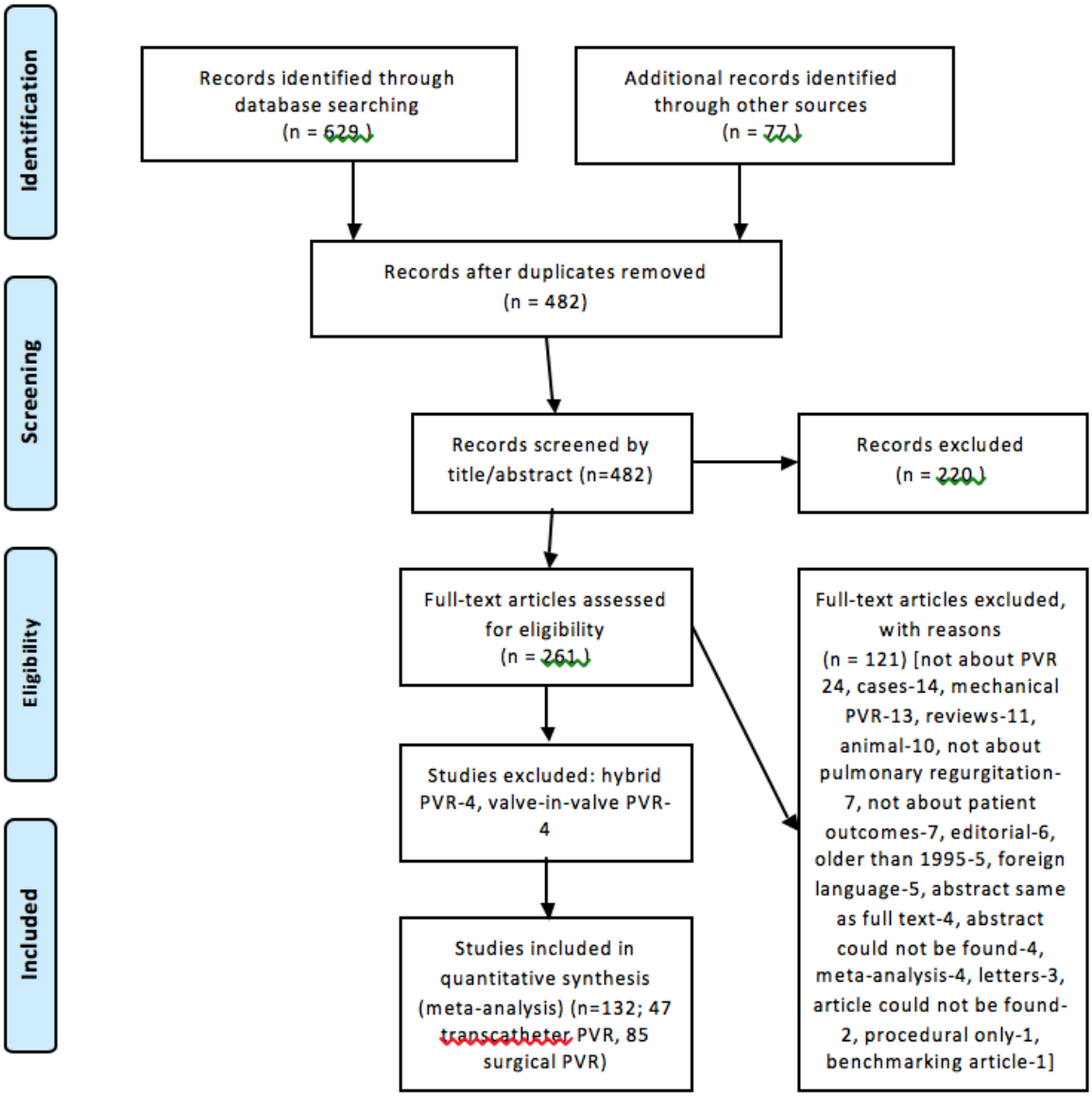

Table 1. Search strategy

Item	Approach
Search terms	Pulmonary valve replacement OR transcatheter pulmonary valve replacement OR hybrid pulmonary valve replacement NOT aortic NOT mitral NOT tricuspid"
Databases searched	Pubmed Web of Science Cochrane Central Register of Controlled Trials and Systematic Reviews .clinicaltrials.gov No date limits were placed on the search to avoid excluding in process citations.
Date of search	May 25, 2016
Inclusion criteria on review of title/abstract/article	All studies reporting patient outcomes from surgical, transcatheter, or hybrid pulmonary valve replacement (PVR).
Exclusion criteria on review of title/abstract/article	1. Studies on mechanical PVR 2. Studies that did not examine patient outcomes 3. Studies that examined only immediate implant outcomes (operating room or cardiac catheterization lab outcomes) 4. Studies primarily examining valve durability 5. Studies conducted with a majority of patients with primary right ventricle to pulmonary artery conduit replacements (rather than PVR) 6. Studies conducted with the majority of patient having pulmonic stenosis or mixed pulmonary stenosis/regurgitation as the indication for PVR (the physiology of these patients may be different than patients with pulmonary regurgitation) 7. Studies about pulmonic regurgitation that did not include PVR 8. Review articles 9. Editorials 10. Letters to the editor 11. Animal studies 12. Case series of 3 or fewer patients 13. Surgical PVR studies reported in 1995 or earlier (earlier era surgical results cannot be compared with contemporary TC PVR results). 14. Abstracts not available in English.
Criteria for irretrievability	Article not available at 3 academic libraries (either electronically or in print) or not available through inter-library loan

Table 2. Study characteristics

Authors	Year	Study design	Sample Size	Mean or median age at procedure (years)	Age SD or range at procedure (years)	Follow-up duration (years)	Follow-up duration SD or range (years)	Valve Type
Primarily Native RVOT (10 studies)								
Boudjemline et al[90]	2012	MS	13	NR	NR	2.67	0.33	Melody
Boudjemline et al[91]	2013	MS	52	22.7	9.18	1.4 (peds) 1.35 (adults)	0.79 (peds), 0.63 (adults)	Melody
Cao et al[92]	2014	SS	5	33	9.5	3.4	0.21	Venus P
Cheatham et al[39] *	2016	MS	20	18.5	11-58	0.08	NR	MNOT
Cools et al[40] *	2015	SS	27	13	6.0-44.9	NR	1.17-3.5	Melody/ Sapien
Demkow et al[93] *	2014	SS	10	NR	21-39	0.08-.17	NR	Sapien
Levi et al[94]	2016	SS	23	NR	15-69	0.75	0.42-1	Sapien
Malekzadeh-Milani et al[41]	2014	SS	34	26	10	2.58	1.75-3.42	Melody
Meadows et al[67]	2014	MS	31	24	7-66	1.25	NR	Melody
Momenah et al[95]	2009	MS	13	14.3	10-23	0.33	NR	Melody
Primarily Conduit Implants (37 studies)								
Armstrong et al[64]	2014	MS	120	19.9	9.7	1	NR	Melody
Batra et al[96]	2012	MS	150	21.7	7-53	1	NR	Melody
Berman et al[63]	2014	MS	25	8	3.4-14.4	0-.5	0.08-3.25	Melody
Borik et al[62]	2015	SS	51	20.2	10.8	0.38	0.16	Melody
Buber et al[66]	2013	MS	147	19	1-61	1.58	0.08-5.33	Melody
Butera et al[42]	2013	MS	63	24	11-65	2.5	NR	Melody

Cheatham et al[61]	2015	MS	171	19	7-53	4.5	0.4-7	Melody
Cheung et al[60]	2013	SS	42	25	6-67	2.25	0.17-5.5	Melody
Chowdhury et al[87]	2013	MS	33	30.3	15.1	0.5	NR	Sapien
Coats et al[97]	2007	MS	17	21.2	8.7	CPEX 0.06, MRI 0.05	CPEX 0.003, MRI 0.08	Melody
Eicken et al[59]	2011	MS	102	21.5	16.2-30.1	0.98	0.27-1.06	Melody
Faza et al[43]	2012	SS	33	20.91 Melody 24.98 Sapien	9.25 Melody 24.75 Sapien	0.5	NR	Melody/Sapien
Fraisse et al[58]	2014	MS	64	21.4	10.5-77.3	4.6	0.2-5.2	Melody
Fraisse et al[98]	2014	MS	6	19.7	5-54.8	3.6	1.8-4.4	Melody
Harrild et al[57]	2013	MS	31	19.8	9.4-40	0.5	0.42-1.08	Melody
Hasan et al[99]	2011	MS	23	NR for PVR	NR for PVR	0.24	0.005-3	Melody
Kenny et al[100]	2011	MS	36	30.3	15.1	0.5	NR	Sapien
Khambadkone et al[44]	2005	MS	59	16	9-43	0.8	0.12	Melody
Kostolny et al[101]	2007	MS	152	13.5	9-43	2.1	1.43	Melody
Lindsay et al[38]	2016	SS	174	NR for PVR	NR for PVR	19	NR	Melody/Sapien
Lurz et al[71]	2010	MS	63	22.2	11.5	0.08	NR	Melody
Malekzadeh-Milani et al[41]	2014	SS, MC	34	26	10	2.58	1.75-3.42	Melody
Malekzadeh-Milani, et al[65]	2015	SS	86	23.9	10.5	1.97	1.25	Melody
McElhinney et al[68]	2013	MS	311	22	10-45	2.5	NR	Melody
McElhinney et al[102]	2011	MS	150	19	7-53	2.5	NR	Melody
McElhinney et al[82]	2010	MS	136	19	7-53	NR	NR	Melody
Moiduddin et al[70]	2009	SS	10	NR	10.9-18.3	NR	0.002-0.005	Melody
Morray et al[103]	2013	MS	404	18	3-73	NR	NR	Melody

Muller et al[55]	2014	SS	13 (PR group only)	25.9	NR	0.5	NR	NR
Nordmeyer et al[29]	2008	MS	123	17.9	1.9	NR	NR	Melody
Nordmeyer et al[56]	2011	MS	108	23.2	11.9	1	NR	Melody
Odemis et al[104]	2013	SS	7	22.2	9.57	0.6	0.39	Sapien
Romeih et al[105]	2009	MS	14	15	10-46	1.33	NR	Melody
Vezmar et al[106]	2010	SS	28	14.9	10.9-19	2.3	NR	Melody
Wilson et al[30]	2015	SS	25	34	8.9	3.5	2.1	Sapien
Zahn et al[19]	2009	MS	34	19.4	7.7	2	NR	Melody
Zampi et al[107]	2016	MS	81	16.4	11.7-22.8	NR	NR	Melody
Surgical PVR (85 studies)								
Alvarez-Fuente et al[76]	2016	SS	35	24.2	NR	22.1	6.82	BP
Babu-Narayan et al[108] *	2014	SS	220	32	NR	NR	NR	H, P, BP
Batlivala et al[109]	2012	SS	254	15.6	3.3	4.4	0-20	H. B
Bigdelian et al[110] *	2015	SS	19	12	5.31	NR	NR	P, M
Bokma et al[77] *	2016	MS	157	29	8.3	7.8	4	H
Borowski et al[111]	2004	SS	18	23.6	11.1	NR	NR	H
Buechel et al[75] *	2005	SS	20	13.9	3	5.9	0.6	H
Chalard et al[112] *	2012	SS	21	30.1	14.1	NR	NR	BP
Chen et al[113] *	2012	SS	227	19.4	0.4-58.1	2.3	0.1-14.6	BP, P
Chen et al[25]	2013	SS	161	NR	NR	48.2	NR	BP, P
de Ruijter et al[114] *	2001	SS	16 PVR	9.2	6.7	11.9	5.9	H
de Ruijter et al[115] *	2002	SS	16 PVR	9.25	6.7	NR	6.NR	NR
Discigil et al[116] *	2001	SS	42	22	16.4	7.8	6	H, B
Dos et al[117] *	2009	SS	116	36	11	NR	NR	P, BP

Doughan et al[118]	2005	SS	21	34	9	7	8	H, BP
Dunne et al[119]	2016	MS	114	21	11-35	62	NR	P
Ermis et al[120] *	2012	SS	19	20.3	NR	NR	NR	NR
Eyskens et al[121] *	2000	SS, MC	18	13.5	2.8	1.4	3.1	H
Fiore et al[122] *	2008	SS	82	NR	NR	homografts 49, porcine 20, pericardial 42	homografts 40, porcine 27, pericardial 21	B
Frigiola et al[89]	2012	SS	73	23.6	11.5	1	NR	H
Frigiola et al[123]	2008	SS	71	22	11	1		H
Fukada et al[124]	1997	SS	10	38.9	16.3	5.4	0.1-12.2	BP, P
Gengsakul et al[49]	2007	SS, MC	82	27.9	13.1	8.8	7.5	BP
Geva et al[33]	2010	RCT, SS	64	21	11.0-58	0.5	0-18	BP
Gorter et al[125]	2014	SS	79	31.9	11.1	0.92	NR	B, M
Gursu et al[126] *	2016	SS	15	14.3	4.5	0.5	NR	NR
Hallbergson et al[127]	2015	SS	101	19	5-60	2.5	0.4-156	NR
Harrild et al[57] *	2009	SS, MC	98	24.6	13	6.5	0.1-60.9	NR
Hartz et al[128]	2003	SS	47	14.2	12	14	NR	P
Hazekamp et al[129] *	2001	SS	51	25.7	11.9	1.7	1.4	H
Henkens et al[130] *	2007	SS	27	30.8	8.2	3	0.3-8.0	NR
Ho et al[131]	2015	SS	26	20	7.6	NR	NR	BP, P
Hooft van Huysduyen et al[132] *	2008	SS	30	31.8	9.1	5.5	1.9	NR
Jain et al[133] *	2012	SS	153	33	18-74	8.5	1.9-15	P, BP, BJ
Jang et al[134] *	2012	SS	131	14.8	6.7	4.2	9.65	P, BP
Kane et al[135]	2011	SS	38	33.1	13.2	0.15	0.1-2.3	NR
Kanter et al[136]	2002	SS	93	10.1	6.3	NR	0.4-12.3	H, P
Karamlou et al[137] *	2006	SS, MC	249	subgroup	subgroup	NR	NR	P, BP, H,

				only	only			Polystan
Kenny et al[100] *	2016	SS, MC	32	NR	NR	NR	NR	NR
Kleinveld et al[138] *	2006	SS	10	11.5	2	NR	NR	H, P
Kostolny et al[101]	2007	MS	6	13.5	9-37	2.1	1.43	P, H
Kutty et al[139]	2008	SS	58	12.1	NR	2.5	NR	H, BP
Kwak et al[140]	2010	SS	132	12.8	6.6	3	2,02	BP, P
Lee et al[141]	2012	SS	170	16.7	4.6-60.2	5.9	0.3-13.5	BP, P
Lee et al[142]	2016	SS	119	16.9	5-57.1	2.6	0.1-5.2	PTFE
Lee et al[143] *	2016	SS	61	7	13.5	5.5	0.1-14.3	BP, PTFE, P
Lee et al[144]	2011	SS	181	14.2	9.8	7.3	2.9	P, BP
Li et al[145] *	2013	SS, MC	26	23.6	8.3	2.2	2.5	NR
Lewis et al[52] *	2016	SS	27	32	NR	NR	NR	NR
Lim et al[146] *	2004	SS	58	13.5	9.6	2.5	2.4	B, M
Lindsey et al[147] *	2010	SS	42	8	3	2.2	NR	BP, P, H
McKenzie et al[148]	2014	SS	148	12.6	NR	5	3.9	BP, P, BJ, H
Meijboom et al[149] *	2008	SS	17	27.6	5.8	6.4	4.4	NR
Morales et al[150]	2007	SS	26	20.3	9.8	1.55	1.1	BP
Neukamm et al[151]	2014	SS	56	NR	NR	5	NR	BP
Nordmeyer et al[152]	2009	SS	60	21	10	3.33	100.83	H
Oechslin et al[153] *	1999	SS	60	33	9.3	NR	NR	B
Oosterhof et al[154] *	2007	MS	71	29	23-37	1.6	0.9-5.2	H
Oosterhof et al[36] *	2007	MS	99	4.9	0.1-16	NR	0.2-15	NR
Oosterhof et al[155] *	2006	MS	158	29	13-45	4.2	0.08-16	H
Pijuan-Domenech et al[50] *	2014	SS	20	35	10	NR	NR	BP
Quail et al[78] *	2012	SS, MC	51	19.6	14.1-24.6	1.8	NR	H
Quintessenza et al[156]	2005	MS	41	19.7	64.7	1.5	0.2-3.1	PTFE

Sabates Rotes et al[157] *	2014	SS, MC	278	31.4	16.4	7.3	6.8	P, BP, H
Sabates Rotes et al[158] *	2015	SS	205	32.9	NR	6.7	max 24	NR
Scherptong et al[159] *	2010	MS, MC	90	31.4	10.3	5.5	3.5	H
Schubert et al[160]	2015	SS	84	18.3	0.8-62.1	2.4	0.2-5.6	BP
Shinkawa et al[48]	2010	SS	73	17.3	2.1-64.4	2.6	0.2-8.0	NR
Shinkawa et al[161]	2015	SS	136	13.2	1.3-20.8	10	0.6-19.9	BP, P
Shiokawa et al[162] *	2012	SS	19	26.1	13.6	7.5	6.5	BP
Sterret et al[163]	2014	SS	26	19.7	7.8	1.26	0.56	NR
Therrien et al[164] *	2000	SS	25	13.5	5.7	2.36	2.24	BP
Therrien et al[34] *	2001	MS	70	27.8	11.9	4.7	MR	BP
Therrien et al[73] *	2005	SS	17	34	12	1.75	0.92	BP
Tobler et al[165] *	2012	SS	39	33	20-65	2.4	1.5	P, BC
Tsang et al[166] *	2010	SS	16	24	13	NR	NR	B, H
Tsang et al[51] *	2016	SS	25	23.28	7.42	NE	MR	B, H
Tweddell et al[167] *	2012	SS	122	NR	NR	NR	NR	H, B
van Huysduynen et al[168] *	2005	SS	26	29.2	24.3-39.4	NR	NR	NR
van Straten et al[169] *	2004	SS	25	58.9	17-45.6	1.58	NR	H
van Straten et al[170] *	2005	SS	16	28.7	19.5-45.6	22	NR	H
Vliegen et al[171] *	2002	SS	26	29.2	9	7.4	2.4	NR
Warner et al[172] *	2003	SS	36	15.2	9.2	6.72	3.36	H, B
Yamamura et al[173] *	2016	SS	14	30.1	11.5	NR	NR	NR
Yemets et al[174] *	1997	MS	85	19.6	NR	5.8	0.08-26	P, BP

Legend: AVR-aortic valve replacement; B-bioprosthesis; BJ-bovine jugular; BP-bovine pericardial; H-homograft; M-mechanical; MC-matched control; MNOT-Medtronic Native Outflow Tract; MS-multi-site; MVR-mitral valve replacement; NR-not reported; P-porcine; PR-pulmonary regurgitation; PS-pulmonic stenosis; PTFE-polytetrafluoroethylene-pulmonary valve replacement; RCT-randomized

controlled trial; SS-single site; * studies composed solely of tetralogy of Fallot patients or its variants or a separate tetralogy of Fallot subgroup analyzed separately

MANUSCRIPT II

Monsen KA, Kelechi TJ, McRae ME, Mathiason MA, Martin KS. Nursing Theory, Terminology, and Big Data: Data-driven Discovery of Novel Patterns in Venous Leg Ulcer Wound Prevention. Accepted for publication in Nursing Research October 27, 2017 with minor modifications (to be published in a Special Issue: Theory and Theorizing in Nursing Science).

Data-Driven Discovery through Theory: Using a Research Dataset with the Omaha System to Identify Novel Patterns in Wound Development

Karen A. Monsen

Teresa J. Kelechi

Marion E. McRae

Michelle A. Mathiason

Karen S. Martin

Abstract

Background: Parallel trends in the exponential growth and diversification of nursing theory, nursing terminology, and nursing data enable a convergence of theory- and data-driven discovery in the era of Big Data research. Existing datasets can be viewed through theoretical and terminology perspectives using visualization techniques in order to reveal new patterns and generate hypotheses. The Omaha System is a standardized terminology and meta-model that makes explicit the theoretical perspective of the nursing discipline and enables terminology-theory testing research.

Objective: To explore a large research dataset from a theory-based perspective using the Omaha System. Aim 1: To examine the normalized Omaha System dataset to understand the sample at baseline relative to Omaha System problem terms and outcome measures. Aim 2: To examine relationships within the normalized Omaha System dataset at baseline in predicting adherence. Aim 3: To examine relationships within the normalized Omaha System dataset at baseline in predicting ulcer development.

Method: Variables from a clinical trial were transformed based on Omaha System mapping to derive a theoretical framework for the terminology-theory testing study. The transformed variables were examined using visualization to generate hypotheses and standard inferential statistics to test hypotheses and evaluate model fit.

Results: Findings of all aims revealed novel patterns in the psychosocial characteristics of the sample as drivers of adherence (Mental Health, behavior, OR=1.28, 95% CL (1.02-1.60) (c=.561) and ulcer development (Mental health, behavior OR = 0.65 (0.45-0.93); Neuro-musculo-skeletal functions, status OR = 0.69 (0.47-1.00); Male OR = 3.08 (1.15-8.24); Not Married 2.70 (1.00-7.26) (c=.758)

Conclusion: Findings suggest that the Omaha System was useful in aligning nursing theory and terminology to describe the discipline of nursing in thought and in data and to explicate or evolve new theorizing methodology. Novel findings suggest a relationship between psychosocial factors and wound development. Further research is needed to generate and test hypotheses based on theory that extend scientific investigations using Big Data research methods with existing datasets.

Keywords: Terminology, Theory, Ontology, Big Data, Omaha System

Introduction

Propelled by the critical need to understand and explicate the discipline of nursing in an era of rapid change in healthcare through massive industrialization and advances in technology, the past five decades have seen parallel trends in the exponential growth and diversification of nursing theory, nursing terminology, and nursing data (Bolles, Boellstorff, Dudgeon et al., 2016). Data science methodology is emerging and evolving as Big Data, characterized by massive volumes of diverse data, both structured and unstructured, remains difficult or impossible to process using traditional databases and software technology (Hey, Tansley, & Tolle, 2009; Mayer-Schönberger & Cukier, 2013). Data of interest to nurses are being generated through clinical documentation, medical devices, consumer apps, and social media (Laplante & Laplante, 2016). The very existence of Big Data in nursing now demands a comprehensive understanding of both theory and terminology as researchers explore new frontiers; *enabled and fueled by* vast datasets into a new paradigm of data-driven research (Hey et al., 2009; Mayer-Schönberger & Cukier, 2013). In this paper, we explore data-driven inquiry through the twin lenses of nursing theory and nursing terminology, using a nursing research-generated wound prevention clinical trial dataset (Kelechi, Madisetti, Mueller, Dooley, & Prentice, 2015; Kelechi, Mueller, & Dooley, 2017; Kelechi, Mueller, King, Madisetti, & Prentice, 2015; Kelechi, Mueller, Madisetti, Prentice, & Dooley, 2017).

Nursing Theory. Nursing's rich theoretical heritage has flourished over the course of five decades, and the resulting body of scholarship spans a wide continuum of granularity and perspective, from the broad notions that form nursing's extensive boundaries to the intricate interactions of interpersonal engagement and transformation (Fawcett, 1984; Meleis, 2012). The metaparadigm of nursing "Person, Environment, Health, Nursing" defined the scope and focus of

the discipline within the context of caring, human health, and environmental factors (Fawcett, 1984, p. 84). Reed (1997) further theorized that the metaparadigm concept of nursing has multiple lenses of doing (praxis), knowing (science), and being (ontology) that together describe an "inherent human process of well-being, characterized by manifestations of complexity and integration in human systems (p.78)." Numerous grand theories elaborate on the meanings and mechanism of the metaparadigm concepts (e.g. King, 2007; Meleis, 2012) while mid-level theories describe how nursing interventions affect health outcomes (e.g. McEwen, 2007; Meleis, 2010); and situation-specific theories posit mechanisms of action that can easily be applied in research and practice (e.g. Meleis, 2012). Theoretical discourse continues as nursing grapples with new disciplinary challenges and perspectives in a changing world influenced by data-driven discoveries (Freshwater & Cahill, 2016).

NursingTerminology. In parallel with the scholarship and applications of nursing theory, nursing terminologies emerged, developed, and matured. Beginning in the 1970's, the North American Nursing Diagnosis Association (NANDA) and the Omaha System were among the first terminologies describing , and continuing into the 1980's and 1990's with the Nursing Interventions Classification (NIC), the Nursing Outcomes Classification (NOC), the Home Health Care Classification (HHCC), now Clinical Care Classification (CCC), the Perioperative Nursing Data Set (PNDS), and the International Classification for Nursing Practice (ICNP) evolved (American Nurses Association [ANA], 2012). These terminologies are considered to describe essential elements of the Nursing Minimum Dataset; and as such may be viewed as the essence of nursing. Use of these terminologies within the electronic health record (EHR), survey instruments, or other electronic data collection tools as tools for care planning, clinical

documentation, and research generates large datasets that are becoming important resources for nursing research (ANA, 2012).

Despite the concurrent development of theory and terminologies in nursing, nursing scholarship regarding theory and terminology remain somewhat siloed (Matney, Brewster, Sward, Cloyes, & Staggers, 2011). This theory-terminology study explored two fundamental gaps and how they may be bridged. First, missing from nursing's theoretical discourse is the explicit notion that nursing's data should express (operationalize) theory and be used to contribute to better understanding the theoretical underpinnings of modern nursing science, practice and research. Second, nursing theory as it underlies clinical practice has often been invisible in the EHR and in other datasets generated using terminologies, and thus not available for use in Big Data research due to the divide between thought and mechanics - between understanding things conceptually and getting things done in real life. In other words, there appear to be twin gaps within the discipline of nursing: that theory is missing from terminology and terminology is missing from theory. We further assume that both theory and terminology define the domain of nursing and are essential to advance knowledge discovery in nursing. In this study, we examine the possible theoretical perspective that may be inherent within nursing terminology, and we test that assumption using an existing large dataset, exploratory data analysis methods suitable for pattern discovery, and the Omaha System (Martin, 2005).

The Omaha System is a multi-disciplinary terminology that is unique within nursing because of its broad scope both across disciplines and settings and inclusion of the human health environment as concepts relevant in health and healthcare. It has been described as a middle-range theory for nursing (McEwen, 2007). Congruent with the nursing metaparadigm, the Omaha System is a conceptual arrangement specifying that: 1) Health exists; 2) Persons

(individuals, families, communities) have problems or potential problems with their health; 3) Nurses and the health care team provide services (interventions) to help people with their health; and, 4) Health may change in relationship to those interventions (Fawcett, 1984; Martin, 2005). This patient-centered problem-based relational framework links problems, interventions, and outcomes in a meta-model for health and healthcare that can be used to operationalize typical nursing research questions: *what types of problems do nurses address? what types of interventions do nurses use? what types of outcomes occur in relationship to particular problems and interventions?*(Martin, 2005).

Big Data Methods. Technology has advanced the ability to generate information, which now far exceeds human capacity to analyze and understand it. Since the 1970's, researchers have advocated for the use of exploratory data analysis (EDA) to address this problem because EDA leverages human perception to interpret patterns visually, while statistical models may mask the unique variations that may be discovered using visualization techniques (Dzemyda, Kurasova, & Zilinskas, 2013; Tukey, 1977). The primary visual cortex more effectively distinguishes relationships among shapes and colors; and the frontoinsular and medial frontal cortex subconsciously analyze images according to their proximity, similarity, and enclosure (Dzemyda et al., 2013). Designers, researchers, and scientists have begun employing innovative and interactive EDA techniques together with other data mining methods and algorithms to meet this challenge. Hypotheses generated using visualization and other Big Data methods may be tested for statistical significance and evaluated for clinical significance, thus detecting and validating previously unknown and hidden patterns within large datasets (Dzemyda et al., 2013; Tukey, 1977).

In this study we propose that existing datasets have potential to reveal new knowledge using EDA methods when examined through the combined perspectives of nursing theory and nursing terminology. The notion of marrying the power of theory and terminology in generating new knowledge has been described previously but has not been applied to datasets that were not originally generated using a nursing terminology (McEwen, 2007; Olsen, Baisch, & Monsen, 2017). One existing dataset from a randomized clinical trial on the prevention of venous leg ulcers had been studied based on the notion of inflammation as a causal factor in wound development, without a nursing theoretical lens (Kelechi, Madisetti et al., 2015; Kelechi, Mueller, & Dooley, 2017; Kelechi, Mueller et al. 2015; Kelechi, Mueller, Madisetti et al., 2017). Such clinical trial datasets often exist in archives and may have potential to reveal additional and important new knowledge. We used this existing wound prevention clinical trial dataset to test whether transformation of the dataset using a nursing terminology and EDA methods would lead to novel findings.

Aims of this terminology-theory testing EDA study were accomplished by transforming existing variables into Omaha System Problem Rating Scale for Outcomes scales in order to categorize all variables into the relational structure suggested by the Omaha System as a theoretical basis for the study. The subsequent data-driven analysis addressed three aims. Aim 1: To examine the normalized Omaha System dataset to understand the sample at baseline relative to Omaha System problem terms and outcome measures. Aim 2: To examine relationships within the normalized Omaha System dataset at baseline in predicting adherence. Aim 3: To examine relationships within the normalized Omaha System dataset at baseline in predicting ulcer development.

Methods

This terminology-theory testing study re-analyzed an existing de-identified dataset from a clinical trial on the use of a cooling intervention compared to placebo on the prevention of venous leg ulcers in individuals with severe venous disease (National Institute of Nursing Research (NINR) Award #R01NR012237). Participants were enrolled for 9 months; the primary outcome was incidence of venous leg ulcers during the trial period. Secondary outcomes were reduction in symptoms such as pain, aching and leg heaviness, and improvement in quality of life and disease management self-efficacy. The study was approved by Institutional Review Boards of two universities.

Instrument: The Omaha System

The Omaha System is a research-based information model and terminology that has numerous attributes and functionalities. It is the only multi-disciplinary clinical terminology that taxonomically classifies the whole of health concepts and interventions, and also serves to measure health Knowledge, Behavior, and Status (Martin, 2005). It was selected for this theory-terminology study because it serves as ontology, taxonomy, standardized terminology, classification, relational conceptual framework, and standardized instrument as below.

Ontology: An ontology conceptually describes things that exist or can exist in the world – and thus is a way of seeing and describing the whole (Reed, 1997). In data science an ontology formally names and defines the types, properties, and interrelationships of the entities that exist for a particular domain of discourse: therefore it is a practical application of the philosophical ontology (Wikipedia, n.d.). Examining the multiaxial, hierarchical structure of the Omaha System relative to these definitions shows that the Omaha System meets requirements for an ontology that is meant to define all of health and healthcare concepts, everything that exists or can exist in the human health environment.

Taxonomy: A taxonomy describes lateral and hierarchical relationships between concepts that enable identification of a broader concept from a more granular concept (Rosenbloom, Miller, Johnson, Elkin, & Brown, 2008). The Omaha System is a multi-hierarchical taxonomy that enables identification of problem concepts through signs/symptoms and strengths. The taxonomic structure gives clarity to clinical reasoning and prevents misuse of concepts (Martin, 2005; Rosenbloom et al., 2008).

Standardized terminology: A standardized terminology is formalized language for a particular domain (ANA, 2012; Rosenbloom et al., 2008). In the Omaha System, terms for health and healthcare are defined. The terms are intended for use at the point of care, and within electronic systems. This is in contrast to clinical terminology standards that are intended to be embedded within systems as codes that are not seen by users (ANA, 2012; Martin, 2005; Rosenbloom et al., 2008).

Classification: A classification is a way of limiting and grouping information (Rosenbloom et al., 2008). The Omaha System classifies all of health and healthcare according to the information model using defined terms. Classifications necessarily exclude nuance and retain central aspects of the meaning by forcing decisions about grouping within pre-determined classes (Martin, 2005; Rosenbloom et al., 2008).

Relational conceptual framework: The notion of establishing relationships between defined problem concepts (problem list), interventions, and outcomes is a goal of the modern EHR (Martin, 2005). The Omaha System relates a structured problem list to an intervention classification and three Likert-type ordinal scales to measure outcomes (1=lowest, 5=highest for dimensions of Knowledge, Behavior, and Status) (Martin, 2005).

Standardized instrument: The Omaha System consists of three inter-related components that are standardized instruments with validated psychometric properties: The Problem Classification Scheme, The Intervention Scheme, and The Problem Rating Scale for Outcomes (Martin, 2005). The Problem Classification Scheme consists of 42 problem concepts arranged in four Domains (Environmental, Psychosocial, Physiological, and Health-related Behaviors) (Appendix A). Each problem concept is defined and has a unique, taxonomic set of signs/symptoms. Variables in this study were transformed using the Problem Rating Scale for Outcomes, which consists of Likert-type ordinal scales for three dimensions of each problem concept: Knowledge (1=no knowledge to 5=superior knowledge); Behavior (1=not appropriate to 5=consistently appropriate); Status (1=extreme signs/symptoms to 5=no signs/symptoms). Given that the KBS scales are applied across all 42 Omaha System problems, the use of these scales levels and normalizes measurement of all health-related concepts. This enables analysis of health and health-related outcomes from a whole-person perspective. The Intervention Scheme addresses any problem concept, and consists of Category (action term: Teaching, guidance, and counseling; Treatments and procedures, Case management; and Surveillance), Target (75 defined terms e.g. coping skills, medication administration), and Care description (customizable details) terms (Martin, 2005). These three instruments rephrase the nursing metaparadigm: Nurses provide interventions to help people with their health problems that are expected to influence health for the better (Martin, 2005; Fawcett, 1984).

Data transformation. The de-identified dataset from a clinical trial on the use of a cooling intervention compared to placebo on the prevention of venous leg ulcers in individuals with severe venous disease (NINR Award#R01NR012237) provided the data for the study. The original data were stored in REDCap, and were transferred for use in this study in excel format

using a secure file sharing application. Initial screening data from participants comprised the independent variables, with two dependent variables being adherence (log data) and development of a venous leg ulcer during the study. Data from patient logs were daily self-report diaries on treatment times, frequency and length. High quality logs were defined as those describing 85% or greater adherence to the study protocol.

Transformation of the existing dataset was accomplished using a content expert approach (Monsen, Holland, Fung-Houger, & Vanderboom, 2014). This data dictionary-terminology mapping exercise was conducted in four steps using Omaha System Problem Rating Scale for Outcomes Knowledge, Behavior, or Status scale-specific ratings. A nursing doctoral student with expertise in cardiovascular nursing and the Omaha System and performed the initial mapping based on Omaha System definitions (Martin, 2005). The student categorized all study variables as described in the data dictionary, including each scale item in all instruments in the database, according to the Omaha System Problem Classification Scheme and Problem Rating Scale for Outcomes. The research team reviewed it and differences were resolved by consensus. For example, blood flow as measured by laser Doppler perfusion was mapped to Circulation Status; items and overall scores in the VEINES-QOL/Sym (Lamping, Schroter, Kurz, Kahn, & Abenhaim, 2003) were mapped to Circulation Status, Interpersonal relationship Behavior, Mental health Behavior, Neuro-muscular skeletal function Status, Pain Status, Role change Behavior, Skin Status, and Social contact Behavior; and the items and overall score for The Self-Efficacy for Managing Chronic Disease Scale (SEMCD-6) (Freund, Gensichen, Goetz, Szecsenyi, & Mahler, 2013) were mapped to Mental health Behavior (see examples in Table 1). A nursing doctoral student with extensive experience in cardiovascular nursing categorized all study variables as described in the data dictionary (including each scale item in all instruments in

the database) according to the Omaha System Problem Classification Scheme. Response scales of all items were converted to the 5-point rating scale used in the Omaha System Problem Rating Scale for Outcomes where 1 indicates the worst (lowest) response and 5 the best (highest) response. Dichotomous items were rated as a 1 (worst) and 5 (best) as related to venous leg ulcers and their prevention. Where possible, existing guidelines for the variable were used (for example standard categorizations of body mass index) (World Health Organization Regional Office for Europe, 2016) or a 5-point index was devised based on available data in the scientific or grey literature (e.g. ankle and calf measurement ranges produced by compression hosiery companies). The categorizations and reference scale were then reviewed by a professor with extensive venous leg ulcer expertise and then by the first author who is an expert in use of the Omaha System and nursing theory. Any differences were reconciled by consensus. The Omaha System data were then summarized and a conceptual model that described the linkage between venous leg ulcers and the Omaha System was developed by the author with venous leg ulcer expertise and refined by discussion with the other authors to reach consensus.

Data transformations and subsequent statistical analyses were accomplished using SAS v. 9.4. Visualization of the transformed data and results was accomplished using heat maps created in Excel using conditional formatting functionality (Dzemyda et al., 2013).

Results

Data-derived Theoretical Framework. There were 95 variables (demographics, temperature measures, anthropometrics, and standardized instruments) in the wound dataset that were transformed into 14 Problem-related Behavior or Status scales (Figure 1; Appendix A). The most common problem was Circulation (29 measures), followed by Medication regimen (14), Mental health (11), and Skin (10). All Domains were represented, with a range of 1-5 Problems

per Domain. Variables in three of the four Domains were transformed to Status scores, with only the Psychosocial Domain having Behavior scores. The proposed theoretical framework derived from the mapping to the Omaha System is an ecological framework consistent with King (2007) and Olsen and colleagues (2017), showing that the physiological problem of potential for wound development exists within the context of other physiological factors (particularly Circulation and Pain). A holistic human experience was depicted in a model derived from the data elements (Figure 1), suggesting that the potential for wound development may influence and/or be influenced by Health-related behaviors Domain factors (particularly Medication regimen and Physical activity factors); Psychosocial Domain factors (particularly Mental health factors) and/or Environmental Domain factors (particularly Income factors).

This study examined the transformed data in three aims. Aim 1 was to examine the normalized Omaha System dataset to understand the sample at baseline relative to Omaha System problem terms and outcome measures. Overall, participants (N=248 who had all adherence information) in the study had significantly higher (better) scores at baseline in the Physiological Domain [3.70 (0.46)], and the Health-related Behaviors Domain [3.67 (0.65)] compared to the Psychosocial Domain [3.23 (0.81)] ($p<.001$ for both). Problems with the highest scores at baseline were Medication regimen [Status, 4.10 (0.59)], Interpersonal relationship [Behavior, 4.20 (1.15)], Neuro-musculo-skeletal function [Status, 4.38 (0.42)], and Urinary function [Status, 4.64 (1.14)]. Problems with the lowest scores at baseline were Role Change [Behavior, 2.49 (1.44)], and Social contact [Behavior, 2.76 (1.11)] (Table 2).

Examination of overall Behavior scores (M=3.4, SD=.9; inconsistently to usually appropriate behavior) vs. overall Status scores (M=3.5, SD=.4; moderate-minimal signs/symptoms) overall showed no significant difference between Behavior and Status at

baseline (t=.44, p=.66); however there was a much wider distribution of Behavior scores at both ends of the scale compared to Status scores which were more centrally distributed. Status scores were distributed across Environmental, Physiological, and Health-related Behaviors Domains, while all Behavior scores were in the Psychosocial Domain.

Visualization of items for analysis in Aims 2 and 3 using heat maps reveals a pattern that predicted both adherence (Figure 2) and prevented ulcer development (Figure 3):

- On a scale of one to ten, how confident are you that you can do things other than just taking medication to reduce how much your illness affects your everyday life?
- On a scale of one to ten, how confident are you that you can keep any other symptoms or health problems you have from interfering with the things you want to do?
- On a scale of one to ten, how confident are you that you can do the different tasks and activities needed to manage your health condition so as to reduce your need to see a doctor?

Aim 2 was to examine relationships within the normalized Omaha System dataset at baseline in predicting adherence (Table 3). Mental health behavior was a predictor of adherence to the study protocol as determined by log quality (Table 4).

When testing for differences in groups based on log quality, no differences were found in domains or problems. The area under the curve was c = 0.561 for the model predicting adherence (Figure 4).

Aim 3 was to examine relationships within the normalized Omaha System dataset at baseline in predicting ulcer development (Table 5). Using t-test to compare Problems by Domain

and Domains, only Skin was statistically different between subjects that developed ulcers and subjects without new ulcers (p=.02) (Table 6). The final multivariate model to predict development of a new ulcer showed that participants scoring better on the Mental health behavior scale and the Neuro-musculo-skeletal function scale were less likely to develop a new ulcer doing the study. Being female and married also lowered participants' likelihood of ulcer development. The area under the curve was c = 0.758 for the model predicting ulcer development (Figure 5).

Discussion

In this theory-terminology study we transformed an extant atheoretical research dataset to a theory-based dataset as an exemplar of pattern discovery (Big Data) research using the Omaha System. Analysis of transformed data from the wound prevention clinical trial revealed novel findings and highlighted the value of this theoretical approach to data-driven discovery. The researchers' implicit model based on physiological processes was that skin inflammation is associated with impaired circulation, which may predispose wound development and result in diminished health and lower quality of life. The comprehensive holistic view of wound care emerged from variable mapping demonstrated that the Omaha System enabled synthesis of a whole person perspective by classifying, leveling, and normalizing all data, and thus provided an underlying conceptual structure for operationalization in Big Data analysis. The findings of the logistic models partially supported the proposed ecological framework. The data-driven analysis revealed compelling evidence of the importance factors in the Psychosocial Domain.

The findings from Aim 1, examining the leveled, normalized data through the ontological lens of the Omaha System, revealed that Social contact and Role change – Psychosocial Domain concepts – had the lowest scores of all concepts at baseline and indicate serious concerns

regarding these social determinants of health (Institute of Medicine, 2014). This is an important finding as most research on characteristics of individuals with leg ulcers focuses on risk factors and physical function; few studies have addressed psychosocial factors (Finlayson, Wu, & Brown, 2015). Our findings suggest that social functioning, such as attending family functions, visiting neighbors, or participating in leisure activities is severely limited. There were also significant reductions in time spent on work and other activities such as volunteering, negatively affecting individual roles. This finding is consistent with a recent study of individuals with varicose veins in which almost 50% reported difficulty at work (Mallick, Lal, & Daugherty, 2017) and quality of life is much lower in individuals who have to limit their activity due to having venous disease or leg ulcers (Tracz, Zamojska, Modrzejewski, Zaborski, & Grzesiak, 2015). Psychosocial problems, specifically the Social contact and Role change problems experience by this population should be further studied, as these may be actionable from a nursing care perspective. Future studies should incorporate psychosocial interventions as needed along with the physiological intervention that predominantly target wound healing outcomes. The fact that Interpersonal relationship, another Psychosocial Domain concept, was one of the highest scores suggests that there may be a protective factor or strength due to positive relationships with friends, family, or other informal supports that may be leveraged to improve outcomes (Monsen et al., 2014). The finding that there was a much wider distribution of Behavior scores at both ends of the scale compared to Status scores suggests that the wider variability of Behavior scores would have more potential for discovery of patterns in Behavior items.

The finding from Aims 2 and 3 that participants were more *likely to adhere to treatment* and *less likely to develop an ulcer* when they expressed *confidence in their ability* to manage

symptoms and reduce the need for health care suggests a relationship between psychosocial factors (strengths and resilience) and multiple outcomes. Studies suggest that having a better understanding of venous disease and risk factors for developing ulcers, from information provided by wound professionals has major implications in changing health behaviors and self-management adherence (Kapp & Miller, 2015; Brown 2014). Disease-specific, patient-focused validated instruments which provide objective measures of interventions designed to increase self-efficacy are particularly useful in clinical practice, however, they are rarely used with regard to leg ulcer patients (Brown, Kendall, Flanagan & Cottee, 2014). This novel pattern should be further explored in future clinical trials using validated instruments.

While the self-efficacy finding, specifically around confidence of the participant in self-care and self-management is novel for this study, previous studies have shown that a strengths-based approach that builds and leverages positive individual, family, and/or community assets such as confidence may benefit older adults with chronic conditions (Monsen, Vanderboom, Olson, Larson, & Holland, 2017). These findings suggest that strengths-based intervention approach should be emphasized to support confidence as part of future trials as well as in practice.

Further, in the Aim 3 evaluation of baseline factors related to ulcer development, the final logistic model finding that non-married males and were more likely to develop an ulcer is consistent with other literature regarding the vulnerability of non-married older males. Being married provides health benefits; morbidity and mortality data suggest married individuals have longer survival times and lower incidence of health conditions compared to unmarried individuals (August & Sorkin, 2010). Having a spouse or partner as a social support who provides reminders to practice self-care or who may assist with intervention may serve as a

protective factor for males. Males in our study developed ulcers more frequently which is in contrast to previous findings in which females are at higher risk (Lohr & Bush, 2013). These findings suggest that it is paramount to address any underlying psychosocial needs as well as physiological needs both in research and in practice, especially for non-married males. Alternative explanations for these findings are a) that it could be that the cryotherapy intervention was more successful for females because they may be more physiologically sensitive (have more thermal receptors) to the effects of cooling (Inoue, Gerrett, & Ichinose-Kuwahara, 2016); or b) study participants may have been better at general self-care because they were being followed in the study (Hawthorne effect, Kelechi, Mueller, Madisetti, et al., 2017).

Implications for research and practice. This study suggests that nursing theory and nursing terminology may be useful for management of Big Data and any existing datasets for nursing research. The existence of large datasets challenges us to think differently about theory. We are challenged by the very existence of the data to employ Big Data methods and seek to understand patterns that may exist in the data (Hey et al., 2009). Given that nursing theorists, terminologists, and researchers have the same end goal – that of understanding and describing nursing – it is incumbent upon scholars to generate discourse in a shared theory-terminology space using Big Data methods and large data sets from clinical trials, other research, and clinician-generated EHR data. This is the first study to examine a nursing terminology as bridge between data and theory (Figure 1). The findings relative to the importance of factors in the Psychosocial Domain for predicting factors in both the Health-related Behaviors Domain (adherence) and Physiological Domain (ulcers) align with ecological framework suggested by the variables; suggesting congruence between nursing terminology and nursing theory and

supporting the operationalization and generation of theory from data using the Omaha System. Further study is needed to extend this inquiry to test other theories, terminologies and datasets.

With respect to using visualization techniques to discover patterns in the data, this technique is more common in the clinical practice of wound care vs. wound care research. Wound care nurses and other professionals are comfortable with the increasing use of visual "clinical" data such as photographs to show patterns in healing progression (Stockton, McMillan, Storey, David, & Kimble, 2015). Our study provides a parallel example of the use of visual patterns in research data that enable novel pattern detection as a useful method for wound care researchers that further validates the need to integrate new methods to advance conceptualizations of theory, terminology, research, and practice in the science of nursing.

Reed (1997) proposed that ontologies can unite theoretical and practical aspects of a discipline. Doing so creates a novel opportunity to build theoretical discourse and advances a method of conceptually describing, explaining and predicting nursing phenomena based on large nursing datasets, thereby enriching the theoretical underpinnings of nursing and linking theory, practice, and research. Our findings suggest that the Omaha System, in accordance with the discourse envisioned by Reed (1997) and other theorists, terminologists, educators and scholars, is an ontological bridge that creates an aligned space in which ideas become data, data becomes knowledge, knowledge becomes wisdom, and "nurse theorists are theorists of nursing in its fullest sense, and likewise nurse researchers are researchers of nursing, and nurse practitioners are practitioners of nursing" (Reed, 1997, p. 76).

Conclusion

This this theory-terminology study examined existing data using Big Data visualization methods and the Omaha System. Findings suggest that nursing theory and terminology align to

describe the discipline of nursing in thought and in data, with important implications for Big Data research in nursing. Pattern discovery within an existing wound prevention clinical trial dataset and subsequent hypothesis testing suggest a relationship between psychosocial factors and wound development among wound prevention clinical trial participants. Further research is needed to test hypotheses based on terminology and theory that extend scientific investigations, and explicate or evolve data-driven theorizing methodology.

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Table 1. Examples of variable transformation (see Appendix A for all variables)

Instrument or guideline	**Item or measure**	**Omaha System Problem**	**Scale (KBS)**	**1**	**2**	**3**	**4**	**5**
Semcd Self-Efficacy Survey item 4	On a scale of one to ten, how confident are you that you can keep any other symptoms or health problems you have from interfering with the things you want to do?	Mental health	Behavior	1-2	3-4	5-6	7-8	9-10
Veines QO Lsym 26 Survey item 20	During the past 4 weeks to what extent has your leg problem interfered with your normal social activities with family, friends, neighbors or groups?	Social contact	Behavior	Extremely	Quite a bit	Moderately	Slightly	Not at all
VAS Pain	On a scale of zero to ten, with ten being the worst pain possible and	Pain	Status	9-10	7-8	4-6	1-3	0

	zero being no pain at all, how much pain in your legs do you have right now?							
Blood flow (laser doppler perfusion units) in treatment leg	Blood flow (laser doppler perfusion units) in treatment leg	Circulation	Ststus	≤5 mmHg	6-10 mmHg	11-15 mmHg	16-20 mmHg	>20 mmHg

Table 2

	N	Mean	SD	Median
Environmental Domain				
Income (s)	246	3.3	1.1	3
Psychosocial Domain	247	3.2	0.8	3.2
Role Change (b)	247	2.5	1.4	2.2
Social contact (b)	247	2.8	1.1	2.7
Interpersonal relationship (b)	247	4.2	1.2	5
Mental health (b)	247	3.6	0.9	3.7
Physiological Domain	247	3.7	0.5	3.7
Pain (s)	247	3.4	0.9	3.5
Skin (s)	247	3.5	0.7	3.4
Neuro-musculo-skeletal function (s)	247	4.4	0.4	4.4
Circulation (s)	247	3.3	0.5	3.4
Urinary function (s)	247	4.6	1.1	5
Health-related Behaviors Domain	247	3.7	0.7	3.6
Nutrition (s)	247	3.2	0.9	3
Physical Activity (s)	247	3.9	1.8	5
Medication regimen (s)	247	4.1	0.6	4.3

Table 3

	Adherence <85%		Adherence ≥85%		t Value	P-value
	Mean	SD	Mean	SD		
N	80		167			
Environmental Domain						
Income (s)	3.1	1.1	3.4	1.1	1.61	0.107
Psychosocial Domain	3.3	0.8	3.2	0.8	-1.00	0.269
Role Change (b)	2.6	1.5	2.4	1.4	-0.85	0.395
Social contact (b)	2.8	1.1	2.8	1.1	-0.11	0.915
Interpersonal relationship (b)	4.2	1.1	4.2	1.2	-0.21	0.832
Mental health (b)	3.6	0.8	3.7	0.9	0.76	0.446
Physiological Domain	3.7	0.5	3.7	0.5	-0.14	0.868
Pain (s)	3.4	1.1	3.4	0.9	0.05	0.961
Skin (s)	3.5	0.7	3.5	0.7	0.15	0.886
Neuro-musculo-skeletal function (s)	4.4	0.4	4.4	0.4	-0.46	0.643
Circulation (s)	3.4	0.4	3.3	0.5	-0.15	0.862
Urinary function (s)	4.8	1.0	4.6	1.2	-1.00	0.312
Health-related Behaviors Domain	3.7	0.6	3.7	0.7	-0.13	0.928
Nutrition (s)	3.2	0.8	3.3	0.9	0.44	0.629
Physical Activity (s)	3.9	1.8	3.9	1.8	-0.17	0.840
Medication regimen (s)	4.2	0.5	4.1	0.6	-0.95	0.350

Table 4

Predicting Adherence				
	Odds Ratio	95% Confidence Limits		p-value
Mental health(b), 3 components, 1 to 5	1.28	1.02	1.60	0.034

Table 5

	No Ulcer		**Ulcer**		**t Value**	**P-value**
	Mean	**SD**	**Mean**	**SD**		
N	210		23			
Environmental Domain						
Income (s)	3.3	1.1	3.5	1.0	-0.85	0.394
Psychosocial Domain	3.2	0.8	3.3	0.7	-0.08	0.937
Role Change (b)	2.5	1.5	2.2	1.2	1.23	0.220
Social contact (b)	2.8	1.1	2.6	1.1	0.73	0.467
Interpersonal relationship (b)	4.2	1.2	4.3	1.0	-0.26	0.797
Mental health (b)	3.7	0.9	3.4	0.8	1.52	0.129
Physiological Domain	3.7	0.5	3.6	0.4	1.43	0.155
Pain (s)	3.4	0.9	3.2	0.8	1.11	0.269
Skin (s)	3.5	0.7	3.2	0.5	2.43	**0.016**
Neuro-musculo-skeletal function (s)	4.4	0.4	4.3	0.5	1.34	0.180
Circulation (s)	3.3	0.5	3.3	0.4	0.79	0.430
Urinary function (s)	4.6	1.2	4.5	1.4	0.62	0.534
Health-related Behaviors Domain	3.7	0.7	3.6	0.6	0.21	0.833
Nutrition (s)	3.3	0.9	3.2	0.8	0.34	0.735
Physical Activity (s)	3.8	1.9	4.5	1.4	-1.80	0.073
Medication regimen (s)	4.1	0.6	4.1	0.5	-0.05	0.963

Table 6.

Predicting Ulcer				
	Odd Ratio	95% Confidence Limits		p-value
Mental health(b), 3 components, 1 to 5	0.646	0.449	0.929	0.019
Neuro-musculo-skeletal function(s), 2 components, 1 to 5	0.685	0.469	1.002	0.052
Male, reference: female	3.079	1.15	8.239	0.025
Not Married, reference: married or in a marriage-like partnership	2.699	1.004	7.257	0.049

Figure 1.

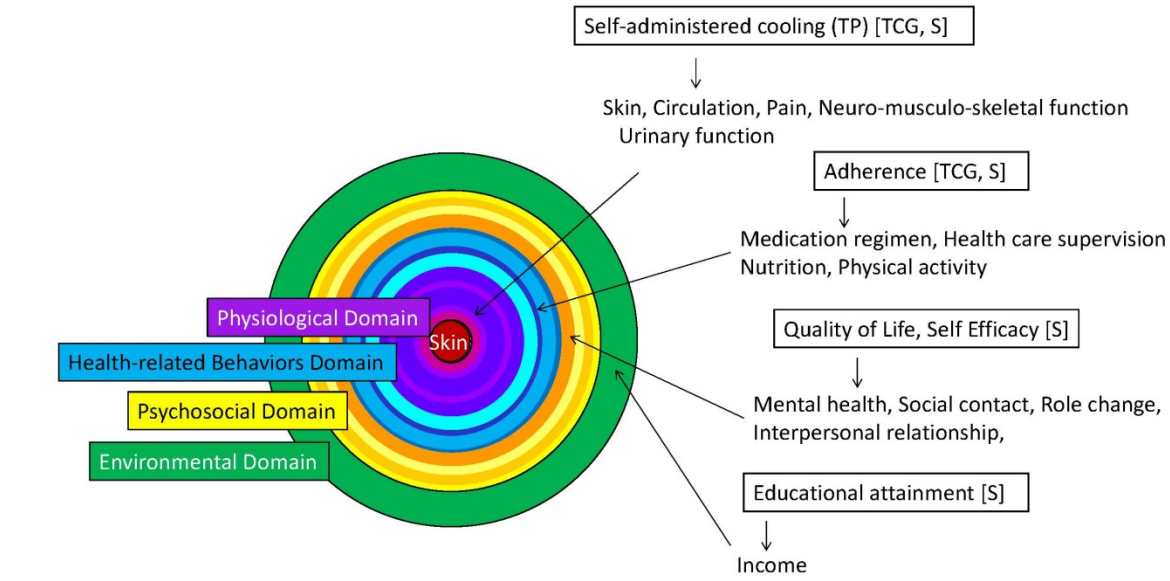
Self-administered cooling (TP) [TCG, S]
Skin, Circulation, Pain, Neuro-musculo-skeletal function
Urinary function
Adherence [TCG, S]
Medication regimen, Health care supervision
Nutrition, Physical activity
Quality of Life, Self Efficacy [S]
Mental health, Social contact, Role change,
Interpersonal relationship,
Educational attainment [S]
Income
Physiological Domain
Skin
Health-related Behaviors Domain
Psychosocial Domain
Environmental Domain
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Figure 2. Heat map for Adherence

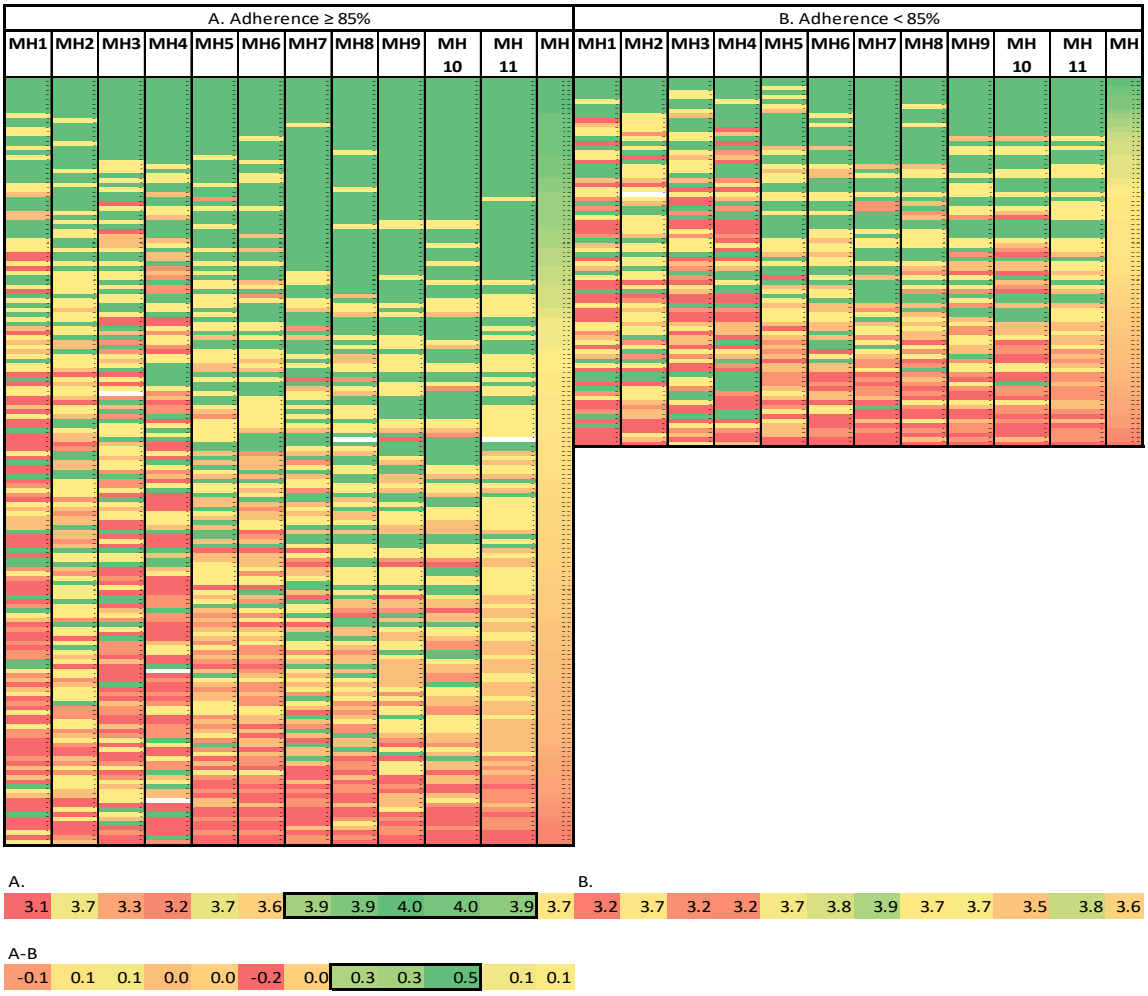

Figure 3. Heat map for Ulcer development

Figure 4

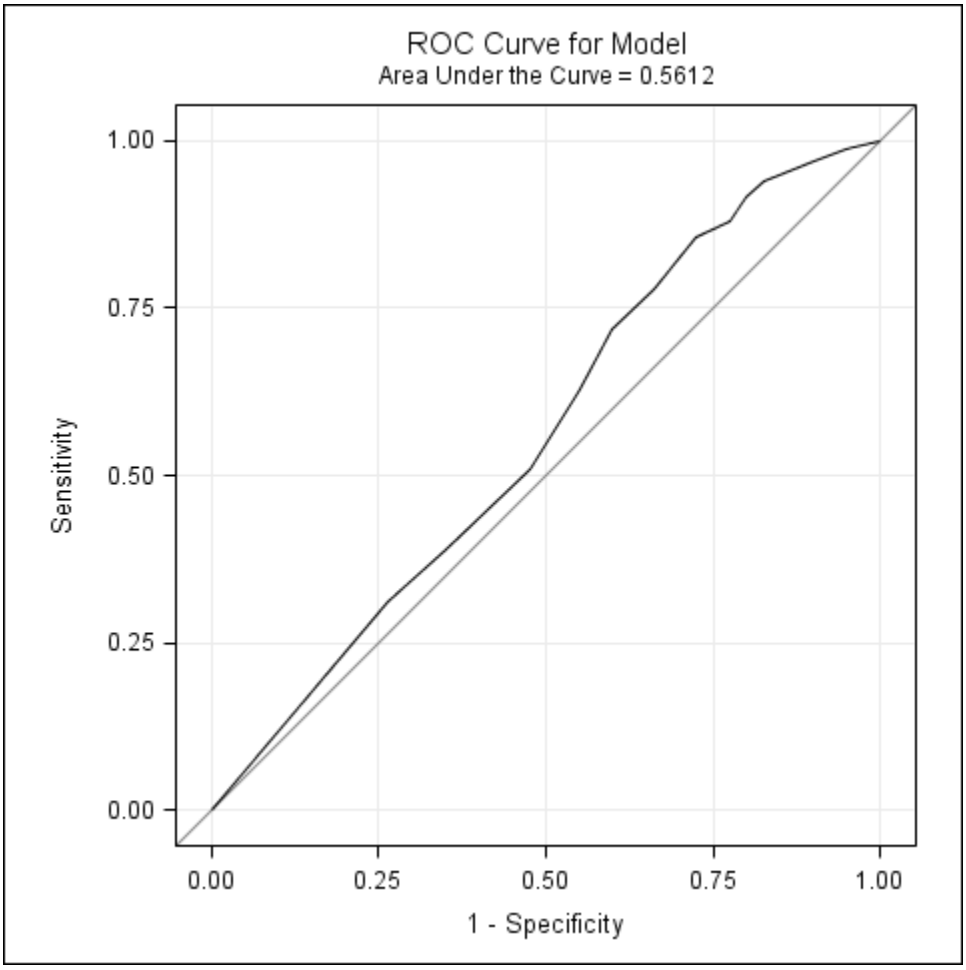
ROC Curve for Model
Area Under the Curve = 0.5612
1.00
0.75
0.50
0.25
0.00
Sensitivity
0.00
0.25
0.50
0.75
1.00
1 - Specificity

Figure 5

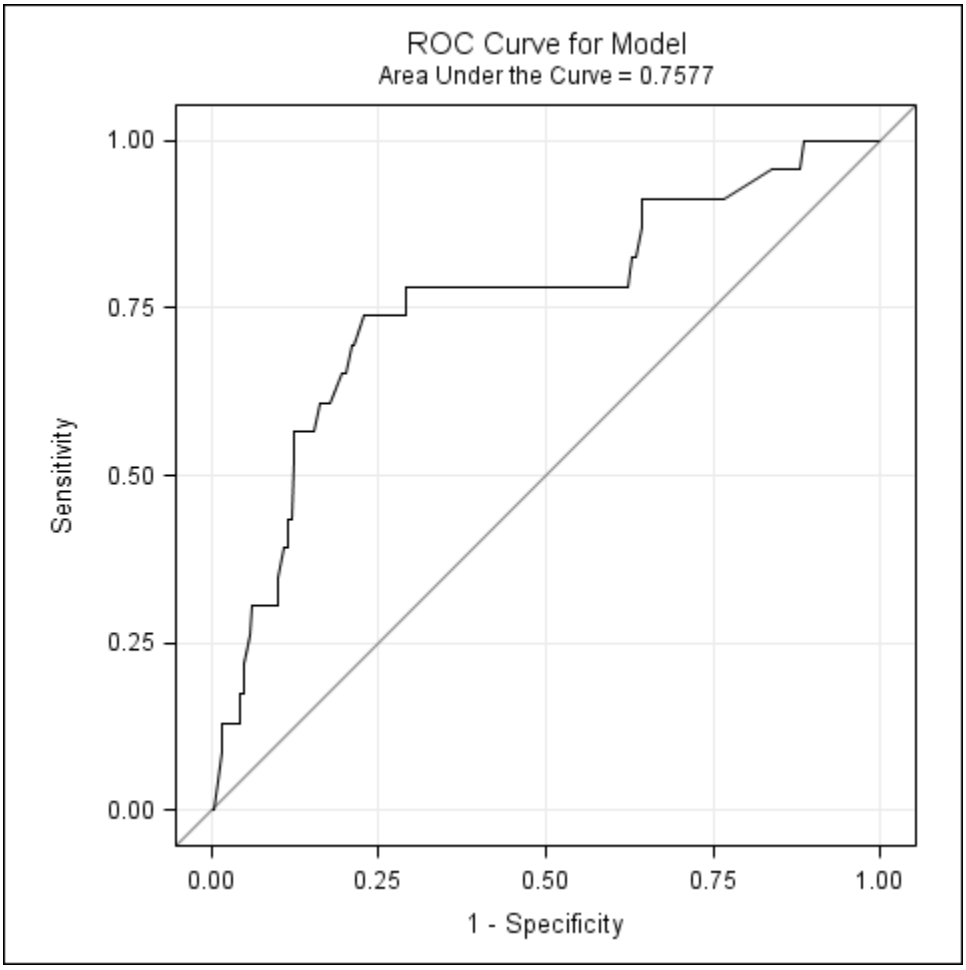
ROC Curve for Model
Area Under the Curve = 0.7577
Sensitivity
1.00
0.75
0.50
0.25
0.00
0.00
0.25
0.50
0.75
1.00
1 - Specificity

Figure Legends

Figure 1. Ecological theoretical framework for wound prevention suggested by the Omaha System variables

Figure 2.

MH1: How much of the time during the past 4 weeks have you felt concerned about the appearance of your leg(s)?

MH2: How much time over the past 4 weeks have you felt irritable?

MH3: How much over the past 4 weeks have you worried about bumping into things?

MH4: How much over the past 4 weeks has the appearance of your leg (s) influenced your choice of clothing?

MH5: On a scale of one to ten, when one is not confident at all and ten is totally confident, how confident are you that you can keep the fatigue caused your disease from interfering with the things you want to do?

MH6: On a scale of one to ten, where one is not confident at all and ten is totally confident, how confident are you that you can keep the physical discomfort or pain of your disease from interfering with the things you want to do?

MH7: On a scale of one to ten, how confident are you that you can keep the emotional distress caused by your disease from interfering with the things you want to do?

MH8: On a scale of one to ten, how confident are you that you can keep any other symptoms or health problems you have from interfering with the things you want to do?

MH9: On a scale of one to ten, how confident are you that you can do the different tasks and activities needed to manage your health condition so as to reduce your need to see a doctor?

MH10: On a scale of one to ten, how confident are you that you can do things other than just taking medication to reduce how much your illness affects your everyday life?

MH11: Total Scale Score MH1-MH10

Figure 3.

MH1: How much of the time during the past 4 weeks have you felt concerned about the appearance of your leg(s)?

MH2: How much time over the past 4 weeks have you felt irritable?

MH3: How much over the past 4 weeks have you worried about bumping into things?

MH4: How much over the past 4 weeks has the appearance of your leg (s) influenced your choice of clothing?

MH5: On a scale of one to ten, when one is not confident at all and ten is totally confident, how confident are you that you can keep the fatigue caused your disease from interfering with the things you want to do?

MH6: On a scale of one to ten, where one is not confident at all and ten is totally confident, how confident are you that you can keep the physical discomfort or pain of your disease from interfering with the things you want to do?

MH7: On a scale of one to ten, how confident are you that you can keep the emotional distress caused by your disease from interfering with the things you want to do?

MH8: On a scale of one to ten, how confident are you that you can keep any other symptoms or health problems you have from interfering with the things you want to do?

MH9: On a scale of one to ten, how confident are you that you can do the different tasks and activities needed to manage your health condition so as to reduce your need to see a doctor?

MH10: On a scale of one to ten, how confident are you that you can do things other than just taking medication to reduce how much your illness affects your everyday life?

MH11: Total Scale Score MH1-MH10

Figure 4. Receiver Operating Curve for adherence

Figure 5. Receiver Operating Curve for ulcers

MANUSCRIPT III

McRae ME, Kelechi TJ, Mueller M, Coleman B, Phillips ABM, Zahn EM. Outcomes of a Novel Approach to Transcatheter and Hybrid Pulmonary Valve Replacement for Congenital Heart Disease in a Single Center. Manuscript to be submitted to Pediatric Cardiology.

Outcomes of a Novel Approach to Transcatheter and Hybrid Pulmonary Valve Replacement for Congenital Heart Disease in a Single Center

Marion E. McRae MScN, ACNP-BC[1,2,3] ORCID ID: 0000-0001-6889-5451
Teresa Kelechi PhD, RN, FAAN[3] ORCID #0000-0001-7412-2607
Martina Mueller PhD[3]
Bernice Coleman PhD, ACNP-BC, FAHA, FAAN[4]
Alistair B. M. Phillips MD, FACS[5]
Evan M. Zahn MD, FACC, FSCAI[2,4]

From: [1]Ronald Reagan UCLA Medical Center, Los Angeles, CA
[2]David Geffen School of Medicine, UCLA, Los Angeles, CA
[3]Medical University of South Carolina College of Nursing, Charleston, SC
[4]Cedars-Sinai Medical Center, Los Angeles, CA
[5]World Federation for Congenital Heart Disease

Corresponding Author: Marion E McRae
Work Address: 7 North CCU, Ronald Reagan UCLA Medical Center, 757 Westwood Plaza, Los Angeles, CA 90095
Work email: memcrae@mednet.ucla.edu
Home email: memcrae1@gmail.com

Acknowledgements:
The authors thank Veena Sivarajan RN, BScN for her audit of coding and data entry.

Abstract

Surgical pulmonary valve replacement (PVR) is the gold standard for treatment of pulmonary regurgitation occurring after treatment of tetralogy of Fallot or pulmonic stenosis. Recently transcatheter (TC) and hybrid PVR have emerged as less invasive treatments. Outcome information after hybrid PVR is largely limited to procedural outcomes. The aim of this study was to assess outcomes for TC PVR (n=32) versus hybrid PVR (n=15) at a single center including procedural outcomes, paired pre- and post-PVR cardiac magnetic resonance, echocardiography, 12 lead electrocardiogram (ECG), arrhythmia outcomes, New York Heart Association (NYHA) Functional Class, cardiopulmonary exercise testing, symptoms, and PedsQL Generic and Cardiac Module health-related quality of life (HRQOL) data to provide data to counsel patients/families on the best approach to PVR. Results were compared to surgical literature outcomes and results from a quasi-meta-analysis of TC and surgical PVR outcomes. Right ventricular end-diastolic volume index decreased for TC and hybrid PVR (both p=.043). Right ventricular end-systolic volume index was decreased in TC PVR (p=.028) but not hybrid PVR. No changes were observed in left or right ventricular systolic function, 12-lead ECG, incidence or types of arrhythmias, or cardiopulmonary exercise capacity. NYHA class improved in the TC PVR group (p<.01) but not the hybrid group. Dyspnea and exercise intolerance decreased. Improvements were seen in most HRQOL measures, but they were non-significant possibly due to limited sample size. Length of stay was 1 day in the TC group and 2 days in the hybrid group where costs were higher. These data provide preliminary guidance for patients selecting PVR strategies. However, findings need to be confirmed in larger samples.

Keywords

Pulmonary valve replacement, transcatheter, hybrid, congenital heart disease, tetralogy of Fallot, pulmonary stenosis

Introduction

Surgical pulmonary valve replacement (PVR) is the gold-standard treatment for pulmonary valve regurgitation and/or stenosis requiring valve replacement. Pediatric surgical PVRs tripled between 2004 and 2012[1] and surgical PVR is now the most common adult CHD cardiac operation.[2] Transcatheter (TC)[3,4] and hybrid PVR[5,6] approaches have been developed as less invasive alternatives to surgical PVR. TC approaches can be used when the right ventricular outflow tract has appropriate anatomy and compliance to support implantation of a balloon expandable valve. Appropriate anatomy includes the absence of risk for coronary[7] or aortic compression[8] by a TC valve. TC approaches consist of valve placement in right ventricular to pulmonary artery conduits, native right ventricular outflow tract implants, or valve-in-valve procedures (valve placement inside a bioprosthetic valve). Hybrid approaches are used when the right ventricular outflow tract is not circular in shape, too large for a TC valve, or when it is difficult to navigate a transcatheter delivery system into place using a transvenous approach. Hybrid approaches to date consist of perventricular access for the procedure,[9] annular remodeling,[6] sternotomy to perform pulmonary artery plication to reduce the pulmonary artery size to that amenable to valve implantation,[5,10] or use of an injectable pulmonary valve via sternotomy or mini-thoracotomy [11-13] with or without pulmonary artery plication.[14] Currently, there are growing reports of TC valve outcomes but reports of hybrid PVR are limited largely to procedural outcomes [5,6,9,11-16] that are often case reports. [5,9,12,13,15] These reports usually do not include any outcome information related to heart remodeling and function, arrhythmias, symptoms, or health-related quality of life (HRQOL). In order to counsel patients about the best approach to PVR, health care professionals need to understand the differences in outcomes of the various PVR approaches.

The aims of this study were to: 1) examine outcomes in all patients who underwent TC and hybrid PVR attempts from mid-2012 (the inception of the Congenital Heart Program) to early 2017 at Cedars-Sinai Medical Center (CSMC) in Los Angeles, CA via analysis of procedural, mid-term, heart remodeling, arrhythmia, symptom, functional capacity, and HRQOL outcomes as well as cost, and 2) to compare TC and hybrid PVR outcomes to surgical PVR to enable health care professionals to better counsel patients/families about the outcomes of these procedures thus allowing them to make better informed procedural choices. As CSMC had a policy of TC and hybrid PVR being tried first, few surgical PVR were performed during this period. Therefore TC and hybrid PVR

were compared to surgical PVR via a quasi-meta-analysis of paired pre- and post-PVR outcomes reported in the surgical literature (n=6196 from 85 studies) [17] and PVR results from the Society for Thoracic Surgeons' (STS)-Congenital Heart Surgery Database (CHSD) and Adult Cardiac Surgery Database (ACSD).[18]

Cedars-Sinai Medical Center (CSMC) developed a novel approach to treating individuals requiring PVR with a bias towards placing the valve in the least invasive manner possible. Procedures started with a cardiac catheterization to obtain data directed at whether a transcatheter (TC) approach was feasible. If thought to be feasible, TC PVR was attempted. If the data obtained (primarily balloon compliance testing of the right ventricular outflow tract) indicated that TC PVR was not feasible or a TCPVR attempt was unsuccessful, a hybrid PVR approach was then undertaken. Only if PVR was not feasible by TC or hybrid approach, traditional surgical PVR was undertaken. This process was done under one anesthetic unless the patient and/or family desired otherwise. Patients identified pre-procedurally as potential hybrid PVR underwent 3D modeling of the right ventricular outflow based upon MRI or CT data prior to the procedure to better plan the PVR. Hybrid procedures were conducted via a small (5 cm) sub-xyphoid incision. Perventricular entry was used to simultaneously place a landing zone stent(s), and, if necessary, 1-3 covered stents (Atrium iCAST stents, Maquet Getinge Group, Germany) to remodel (reduce the circumference) the right ventricular outflow tract to prevent paravalvar regurgitation. The lumens of the covered stents were then occluded with vascular plugs (AVPII, St. Jude Medical, St. Paul, MN) and the TC valve was placed into the center of the landing stent. The hybrid procedure has been previously described in detail.[6] If right ventricular outflow tract remodeling was not possible using these procedures a full sternotomy was performed to permit pulmonary artery plication and implantation of a TC valve.

Materials and Methods

This was a single center, retrospective chart review of adult and pediatric patients undergoing TC and hybrid PVR. There were no specific exclusion criteria for this study. This study was approved by the Institutional Research Board (IRB) of CSMC and by reliance agreement by the IRB of the Medical University of South Carolina via expedited review as it involved retrospective data only.

All comparisons before and after PVR were examined via the use of paired measurements. Heart remodeling and function was examined using pre-and post-PVR cardiac magnetic resonance imaging/angiography (MRI/MRA) and echocardiographic data. Arrhythmias were examined by electrocardiographic data (ECG) as well as Holter/Zio patch data (iRhythm, San Francisco, CA). Symptoms were assessed from self-report and New York

Heart Association (NYHA) Functional Class. Cardiopulmonary exercise test data were used to assess functional capacity. HRQOL was assessed via the PedsQL Quality of Life Inventory[19,20] and PedsQL Cardiac Module[21]). Prior permission was received from the Mapi Research Trust (Paris, France) to use the PedsQL Core Scales and Cardiac Module instruments to assess HRQOL as part of clinical follow-up care. Definitions of complications for TC and hybrid PVR were adapted from Kappetein [22] to be consistent with other TC studies. Definitions for surgical complications were taken from Akins [23] to be consistent with the surgical literature.

All echocardiogram and cardiac MRI/MRA were previously interpreted by a congenital cardiologist with expertise in cardiac MRI/MRA and echocardiography. Values were indexed to body surface area and z scores were calculated to compare pediatric and adult patients. All MRI measures are referenced to normal values developed by Alfakih.[24] Cardiopulmonary exercise tests were conducted on a cycle ergometer and were interpreted by a physician who had expertise in exercise physiology. Arrhythmias were assessed by 7-day Zio patch or 48- hour Holter monitor if insurance would not pay for Zio patches. NYHA Functional Class was assessed by the nurse practitioner and cardiologist performing examinations according to patient self-report of symptoms. Procedural cost information was obtained from the hospital billing department.

Health-related quality of life assessment measures pre- and post-PVR were introduced into the clinical PVR protocol in July 2016 using the generic Pediatric Quality of Life Inventory 4.0 Generic Core Scales (PedsQL^{TM})[19,20] and the Pediatric Quality of Life Inventory (PedsQL^{TM}) 3.0 Cardiac Module,[21] both of which have pediatric and adult forms. The PedsQL Generic Core Scales consist of 23 items that are self-report or interviewer-administrated and measure 4 dimensions of HRQOL over the past month (except at the 1-week post-procedure visit when the time period was 1 week): (1) physical functioning, (2) emotional functioning, (3) social functioning, and (4) school functioning (or school/work for the adult forms). A disease-specific instrument, the PedsQL 3.0 Cardiac Module was used to add disease-specific sensitivity in measurement. This instrument has 27 items and measures 6 dimensions of HRQOL (heart problems and treatment, heart medicine treatment, perceived physical appearance, treatment-related anxiety, cognitive problems, and communication) that are relevant to congenital heart disease.

Both PedsQL instruments use a 5-point Likert scale (3-point Likert scales for the self-report instrument versions for ages < 8years). For children < 8 years of age, the items are read to them and a staff member helps them to fill out the responses according to the standardized administration instructions.[25] Scores are reverse transformed

to 0-100 scales according to scoring instructions [26] with higher scores indicating higher levels of HRQOL. Subscale scores and total scores are computed if at least 50% of the subscale is completed by summing the transformed scores and dividing by the number of items answered. For the PedsQL Core Scale a Psychosocial Health Summary Score is computed with the sum of the transformed items divided by the number of items answered in the Emotional, Social, and School Functioning Scales. A Physical Health Summary Score is equivalent to the Physical Functioning dimension score. Total scores are computed by summing the transformed items from the whole score divided by the numbers of items answered on the total scale with higher scores indicative of higher HRQOL.[26] For developmentally-delayed individuals >18 years who are not capable of completing the tool, the parent/caretaker with the most knowledge of the question content is asked to complete it at clinic visits. Intra-class correlations between the parent and child forms have been found to be fair to good (0.44-0.70) for ages 8 years and over. [27,28,25] The Core Scales have good reliability and validity in CHD patients.[19,20,29,30,21] Limited data using the PedsQL instruments was available due to the recent introduction of its use in clinical practice.

Data were extracted from the electronic health record and entered into a Research Electronic Data Capture (REDCap, Vanderbilt University, Nashville, TN) database designed for protected health information. REDCap is a software toolset and workflow methodology for electronic collection and management of research data.[31] All data entry was checked for accuracy of coding and data entry by a nurse experienced in congenital heart disease and data entry. Any discrepancies were reconciled with the original data. The de-identified data were then downloaded into SPSS Version 24 (IBM, Aronak, NY) for analysis. The data were examined for normality and the assumptions for the planned statistical tests.

Due to the small sample, the emphasis of the statistical analysis was the use of descriptive statistics. Categorical data were summarized with counts and percentages. Ordinal data were summarized with medians and ranges. Interval level and higher data were summarized with means and standard deviations where the data were normal in distribution. In addition, where sufficient data were available, paired t-tests were used for normally-distributed interval level variables pre- and post-PVR. Wilcoxon signed rank tests were used where statistical assumptions were not met to use paired t-tests or where ordinal level measurement was performed. McNemar tests were used to compare proportions of patients with outcomes on nominal level variables. All tests were 2 tailed tests with the level of significance set at $p<.05$.

Results

Sample Characteristics

A total of 50 PVR procedures were attempted on 48 patients with 32 being performed via TC technique and 15 by hybrid technique. Two patients went on to elective surgical PVR, one due to aortic compression noted when a test balloon was inflated in the outflow tract and one due to the small size of a previously implanted pulmonary bioprosthesis that did not permit a TC valve-in-valve procedure (bioprosthesis size was difficult to estimate on cardiac MRI due to artifact and no old surgical notes existed). One subject with hybrid PVR required urgent surgical PVR due to embolization of the stent/valve. One TC PVR attempt was unsuccessful and the patient/family elected to come back on another day and underwent a successful hybrid PVR. Twelve TC PVR were performed in "native outflow" tracts, 7 were valve-in-valve procedures, and 13 were implants in right ventricular to pulmonary artery conduits. All hybrid PVR were performed in "native" outflow tracts, 6 were perventricular implants, 7 of these required annular remodeling of the native right ventricular outflow tract, and 2 required full sternotomy for pulmonary artery plication to place the largest available valve. Subject demographic and clinical variables are summarized in Table 1.

This was a predominately White, non-Hispanic cohort with 14 pediatric and 36 adult procedures. Ten patients (approximately 20% of patients) had known genetic syndromes, seven of those underwent TC and three underwent hybrid PVR (four with 22q11.2 deletion, two with Down syndrome, one with Goldenhaar syndrome, one with 17p deletion [Smith-Magenis syndrome], one with 10p22 and 10q23 deletion, and one with a 6q14.3 duplication of unknown significance). There were two other hybrid patients with possible genetic syndromes, but no previous genetic testing had been performed. Ten subjects underwent palliative procedures prior to definitive surgical repair. A larger proportion of the subjects with hybrid PVR (77.3% versus 50.0% of the TC subjects) had undergone a tetralogy of Fallot (TOF) repair with a transannular patch, making the right ventricular outflow tract dimensions too large for current TC valves. Consistent with this finding all but one hybrid subject had a primary indication for PVR of pulmonary regurgitation prior to the procedure whereas 60% of the TC group had the TC group had pulmonary regurgitation as an indication (versus 40% pulmonary stenosis). For 18 subjects, the current procedure was a repeat PVR (16 TC PVR and 2 who went on to surgical PVR).

Procedural Outcomes

Procedural variables and outcomes are reported in Table 2. Procedural outcomes from the initial 10 hybrid PVR are described in a previous publication.[6] Initial implants were unsuccessful in 9.4% of the TC versus 6.7% of the hybrid group. Due to the larger size of the valves needed for the hybrid PVR (predominantly 29 mm valves), 86.7% of these procedures were performed with Edwards Sapien XT and S3 valves (Edwards Lifesciences, Irvine, CA) versus the TC procedures where only 53.1% of the procedures required the larger valves. Therefore, more Medtronic Melody valves (Medtronic, Minneapolis, MN) were used in the TC group. The three patients with surgical PVRs all went on cardiopulmonary bypass but only one required aortic cross-clamping. Procedural time and radiation exposure was significantly higher in hybrid cases versus TC cases, but fluoroscopy time was similar between the groups.

Complications included one patient with procedural arrhythmias (runs of ventricular tachycardia) that did not require treatment with drugs or cardioversion (hybrid PVR). Minor complications included three TC patients who had bleeding from the catheterization site treated with resumption of site pressure. Three access-related vascular complications [22] occurred (one wire perforation and two contained dissections). Four patients required blood transfusion (one for wire perforation [TC PVR], one hybrid PVR patient was autotransfused during the procedure, one TC PVR subject who was critically ill at time of PVR with low platelets and hemoglobin, and one hybrid PVR patient who went on extracorporeal membrane oxygenation [ECMO] one day after the procedure). One asymptomatic pericardial effusion was discovered in a hybrid PVR subject 1 day after the procedure and was treated with pericardiocentesis 6 days post-PVR. Two superficial hybrid incisional infections were treated with oral antibiotics with resolution. Two hybrid PVR patients (one with sternotomy) developed small right apical pneumothoraces that resolved without further treatment. Hypotension treated with vasopressors occurred in one hybrid PVR subject. Migration of a left pulmonary artery stent placed prior to TC PVR occurred in one subject without further sequelae. There was one Stage 1 acute kidney injury (AKI), one Stage II, and one Stage III AKI.[22] One of these patients was listed for heart-kidney transplant prior to the PVR. The other AKIs occurred in two the patients who died, one of whom was critically ill prior to the PVR. The two contrast reactions consisted of rashes, one requiring steroid and diphenhydramine treatment and the other diphenhydramine only. There was one brachial plexus injury in a hybrid PVR that quickly resolved. Tricuspid valve chordal rupture (with mild-moderate tricuspid regurgitation) occurred in three hybrid patients despite use of transesophageal echocardiography to guide insertion

of the delivery sheath to avoid the tricuspid valve apparatus. One case of chronic pain syndrome lasting several months occurred in a hybrid PVR subject likely due to undertreatment of post-procedural pain in an obese woman.

Length of stay was a median of 2 days in the hybrid procedures versus 1 day in the TC patients. There was one death in both in the TC and hybrid groups. The death in the TC PVR group was a 36-year old male with atrial and ventricular septal defects with pulmonary hypertension, severe heart failure, sepsis, an ischemic stroke, and renal failure who arrived at CSMC in extremis pre-PVR. He underwent TC PVR 10 days later as a salvage attempt and died 21 days post-PVR of cardiogenic shock, sepsis, and right ventricular failure unrelated to any procedural complications. The death in the hybrid PVR group occurred in a 36-year old developmentally-delayed female who had embolization of the stents/valve to the main pulmonary artery and conversion to surgical PVR and removal of the embolized items. Her intraoperative surgical course was uneventful, and she was stable throughout. She was extubated shortly after surgery. For unclear reasons she experienced a cardiac arrest on postoperative day 1, was placed on ECMO, and ultimately died 5 days post-PVR.

Mid-term Outcomes

Mid-term outcomes are shown in Table 3. Follow-up was complete in 68.8% of TC and 73.3% of hybrid patients. The primary reasons for lack of follow-up were insurance issues, patients living at a distance who did not want to return for follow-up, and follow-up by outside cardiologists.

In addition to the above two deaths described under 30-day mortality there was one death in a 32-year old male who in addition to a hybrid PVR with annular remodeling had a transcatheter ASD and PFO closure with 2 Amplatzer devices during the same procedure. He died 11 months post-procedure from unknown causes. Of note, all 3 deaths after PVR occurred in patients with significant developmental delay (one with Down syndrome, one with cerebral palsy, and one with a likely genetic syndrome with no prior testing).

There were no reported cases of infective endocarditis. There were 2 patients who underwent a second valve implant during the study period. One was in a 6-year-old female with a TC #26 Sapien PVR that became severely regurgitant 24 months after implantation. Her Sapien valve was replaced with a Melody PVR. The second was in a TC subject with an unusual kinked right ventricular to pulmonary artery conduit who developed early re-stenosis and required a stent reconstruction and re-valving in another location within her right ventricular outflow tract 5 months

after the initial implant. One Type 1 stent fracture[32] was noted 52 months after implant in a TC PVR (valve-in-valve) subject without apparent clinical importance.

Cardiac MRI/MRA and Echocardiographic Outcomes

Cardiac MRI/MRA outcomes were assessed pre- and post-PVR with the post-PVR measurements conducted at a median of 679 days (range 273-1227) and 366 days (range 264-812) post-PVR in the TC and hybrid groups respectively. A total of 53 MRI/MRAs were performed but only 14 were paired MRI/MRA measurements (2 with pulmonic stenosis physiology and 12 with pulmonary regurgitation physiology). Cardiac MRI/MRA results are shown in Table 4. Right ventricular end-diastolic volume index (RVEDVI) was significantly decreased in both TC and hybrid PVR (both $p=0.043$). Regurgitant fraction (RF) was statistically reduced in TC PVR ($p=0.028$) but not hybrid PVR despite a reduction from a median of 46% to 2%, which is a clinically significant reduction but was not statistically significant. Right ventricular end-systolic volume index (RVESVI) was significantly reduced with TC ($p=0.028$) but not hybrid PVR. There was a reduction in the proportion of patients with right atrial enlargement on MRI from 50% to 25% in the TC group and from 75% to 0% in the hybrid group, but the results were not statistically significant. The remainder of the examined values did not change significantly after TC or hybrid PVR.

Echocardiography outcomes are shown in Table 5. Post-PVR measurements were performed at a median of 320 days (range 30-1185) and 356.5 days (range 14-1239) after PVR in the TC and hybrid groups respectively. There was a significant improvement in qualitative right ventricular ejection fraction (RVEF) in the TC group ($p=0.03$) but not in the hybrid group ($p=0.35$). Both TC and hybrid PVR had a significant reduction in pulmonary regurgitation (both $p<0.01$). Left ventricular end-diastolic volume index (LVEDVI) improved significantly ($p=0.02$) in the TC but not the hybrid group ($p=0.09$). Although there were some cases of paravalvar regurgitation in the hybrid group post-PVR there was no significant difference between pre- and post-PVR as assessed by McNemar's test ($p=0.125$). The remainder of the assessed indices did not change significantly. In addition to assessment of MRI and echocardiogram outcomes by PVR type, outcomes were also assessed by primary physiology pre-PVR (pulmonary regurgitation versus pulmonary stenosis) and there were no significant differences (results not shown) between the results as assessed by procedure type.

Electrocardiogram (ECG) and Arrhythmia Outcomes

ECG outcomes were assessed at a median of 268 days (range 9-1318) and 208.5 days (range 6-772) post-PVR in the TC and hybrid groups respectively and are shown in Table 6. There were no significant changes in QRS duration, PR interval, or QT interval after PVR. The QRS duration was higher in the hybrid group versus the TC group at baseline (hybrid: 152.7 ± 16.5 versus TC 127.4 ± 36.5) This finding persisted post-PVR. Similarly, the QTc durations were larger in the hybrid group both pre- and post-PVR. Arrhythmia outcomes as assessed by Holter monitor or Zio patch were performed at a median of 710 days (range 2-1564) and 383 days (range 7-457) post-PVR in the TC and hybrid groups respectively. There were 21 Holter monitors (24 or 48 hour) performed and 19 7-day Zio patches. However, there were only 9 subjects with pre- and post-PVR monitors. Due to the small numbers of patients with pre- and post-PVR Holter and Zio patches, results were assessed for the whole group of subjects, not by TC versus hybrid PVR. No changes in arrhythmias pre- and post-PVR were noted for either TC or hybrid PVR.

Cardiopulmonary Exercise and NYHA Functional Class Outcomes

Twenty-eight cardiopulmonary exercise tests were conducted but there were only 5 paired pre- and post-PVR tests (see Table 8). Cardiopulmonary exercise test results were assessed at a median of 835 (range 349-1217) and 484 (range 400-447) days post-PVR in the TC and hybrid groups respectively. There were no significant changes seen in the parameters assessed.

NYHA functional class outcomes were assessed at a median of 268 days (range 9-1318) and 208.5 days (range 18-772) post-PVR in the TC and hybrid groups respectively (see Table 9). There was a significant improvement in NYHA functional class in the TC group ($p<0.01$) indicating improvement in functional capacity. Although NYHA functional class was improved in the hybrid group it did not achieve statistical significance ($p=0.11$).

Symptom Outcomes

Symptoms were assessed at a median of 268 days (range 3-1500) and 374 days (range 7-457) post-PVR in the TC and hybrid groups respectively. When both TC and hybrid PVR results were examined as one group there was a significant decrease in dyspnea on exertion ($p=0.01$) and exercise intolerance ($p=0.02$). However, when symptoms were broken down by TC versus hybrid there was no significant difference between pre- and post-PVR (see Table 10).

HRQOL Outcomes

There was limited HRQOL data available as the PedsQL was only used since July 2016. There were a total of 31 PedsQL instrument pairs (Core Scales and Cardiac Module) completed but only 7 subjects had pre-PVR and post-PVR measures performed and these were performed at a median of 10 (range 3-122) days post-PVR. Therefore, outcomes measured using the PedsQL are reported for the whole group and not broken down by procedure type (only 1 hybrid PVR in the reported results). Although improvements were seen on the Physical and Psychological Scale Scores on the Generic Scale and on the Health Problems and treatment, perceived physical appearance, treatment anxiety, and cognitive problems subscales on the Cardiac Module, the results were not statistically significant likely owing to the small sample size.

Costs

Direct costs for the PVR procedures were a median of $46,324.50 (range $8,949-$389,994) for TC and $70,701.50 (range $39,772-$124,759) for hybrid PVR. Indirect costs were a median of $19,160 (range $10,363-$352,729) for TC and $29,432.50 (range $19,146-$42,305) for hybrid PVR. Therefore, total costs were a median of $65,485 (range $19,312-$742,723) for TC and $100,035 (range $58,918-$167,064) for hybrid PVR.

Discussion

Procedural Outcomes

Our 30-day mortality of 3.1% for TC PVR is higher than that found in a recent systematic review and meta-analysis of TC PVR at 1.5% (95% CI 0.8-1.6%) for TC PVR.[33] This reflects the use of this therapy in one patient in moribund condition pre-procedurally. Our hybrid PVR mortality was 6.7%. There are no other hybrid PVR series that report mortality. These results compare with surgical mortality of 0.9% between 2007 and 2013 in the STS-CHSD and 4.1% in the STS-ACSD which includes patients who are older with more surgical risk factors and operations performed by non-congenital cardiac surgeons.[18] The deaths (two early, one late) were all in patients with severe developmental delay/genetic syndromes. There was an assumption by referring physicians that these patients would all need surgical PVR and, due to their developmental delay, would not tolerate the procedure well and therefore referral was deferred. One of these patients had the largest right ventricular volumes of all patients in the study (330 mL/m^2). Another patient was referred in extremis. Earlier referral of individuals with developmental delay/genetic syndromes should occur to facilitate a successful TC or hybrid approach and is imperative to

improving results in this group of patients. This is particularly important in Down Syndrome where pulmonary arterial hypertension is common and may lead to more rapid right ventricular dilatation.[34]

The stent/valve embolization rate of 3.1% for TC PVR was less than reported in the literature. [33,17] The rate of conversion from hybrid to surgical PVR in our series was 6.7% versus 16.7% in the only other series aside from case reports. [35] Wire perforation at 3.1% was within the confidence intervals reported in a previous meta-analysis. [33] Neither stent/valve embolization or wire perforation are seen with surgical PVR. Blood transfusion in 6.3% of TC PVR reflects transfusion of a moribund patient with multiple hematological abnormalities. The only procedure-related transfusion was in the patient with a wire perforation which would make the procedure-related true transfusion rate 3.1% which is line with previous studies.[33] Blood transfusion in the hybrid group was higher than in the literature [14] reflecting the need for transfusion in the patient who went on ECMO. In comparison, blood transfusion was used in 38% of PVR in the STS-CHSD database and 55% of PVR in the STS-ACSD.[18]

There were no cases of AKI requiring new dialysis with either TC or hybrid PVR, a complication reported in 0.2% of surgical PVR patients in the STS-CHSD database.[18] There were no cases of neurologic deficit persisting at discharge or phrenic nerve injuries in either TC or hybrid PVR patients that occur in 0.6% and 0.3% of patients in the STS-CHSD.

Paravalvar pulmonary regurgitation and possibly valve/stent embolization may be reduced with infundibular reducers that are now entering clinical trials. If these devices are successful, surgical PVR may be increasingly reserved for those with coronary or aortic compression. Tricuspid valve injuries occurred in three hybrid patients and resulted in mild-moderate tricuspid regurgitation. This complication has been previously reported in the literature. [16]

Length of stay was a median of 1 day in TC PVR and 2 days in hybrid PVR. Our length of stay was considerably shorter than other reports for hybrid PVR of 6-8 days [11,13,14] but these reports involved sternotomy. This compares with 5 days in the STS-CHSD for surgical PVR. [18] Radiation doses and fluoroscopy times for TC PVR were similar to a previous report.[36] There are no reports of hybrid radiation and fluoroscopy times in the literature.

Mid-Term Outcomes

There were no cases of infective endocarditis in either TC or hybrid PVR. As follow-up is short in this cohort this could increase with further follow-up time. We advised all our patients to stay on aspirin 81 mg daily

and continually re-emphasized reporting unexplained fevers and obtaining blood cultures before starting antibiotic therapy. Discontinuation of aspirin therapy has been found to be a risk factor for the development of infective endocarditis with the Melody valve. [37] Our cohort had a 53.1% and 86.7% incidence of Sapien valve use in the TC and hybrid groups respectively which has been associated with a lower risk of infective endocarditis than the Melody valve. [38] This difference may also have influenced the results. Lower rates of infective endocarditis with the Sapien valve versus the Melody valve and in native right ventricular outflow tract PVR versus conduit implants (where the Melody valve is more likely to be used) have been reported by others. [39,38]

Cardiac MRI/MRA and Echocardiography Outcomes

A significant reduction in RVEDVI after both TC PVR and hybrid PVR was seen due to a reduction in pulmonary valve regurgitant fraction. This finding has been well demonstrated in previous studies with TC and surgical PVR.[17] The RVEDVI normalized in the TC PVR group but not the hybrid group likely due to larger initial RVEDVI volumes. Others [40] have reported normalization of RVEDVI after surgical PVR when the pre-PVR RVEDVI does not exceed 165 mL/m2 and our study supports this. One other group has reported a decrease in RF and RVEDVI after hybrid PVR (full sternotomy with implantation of the Shelhigh injectable porcine valve) in 5 patients 6-12 months post-PVR.[35]

With TC PVR there was significant reduction in RVESVI similar to that seen in the meta-analysis. [17] Reduction in RVESVI has been demonstrated in surgical PVR. [41,42] The small numbers of measurements in the hybrid PVR group limited statistical power to detect any difference. Like other studies[17], there was no significant improvement in RVEF measured by MRI in either the TC or hybrid PVR group. However, there was an improvement in qualitatively-measured RVEF in the TC group only by echocardiography. Our finding of a reduction in right atrial size on MRI was not statistically significant, possibly due to the small sample size. We could not find other studies describing right atrial size changes for TC or hybrid PVR. One surgical PVR study demonstrated significantly reduced right atrial volumes post-PVR.[43] Whether this would equate with a lower incidence of atrial arrhythmias over time would be difficult to assess as our incidence of atrial arrhythmias was low to start with.

On echocardiography there was an increase in the LVEDVI, although it was not clinically significant. A previous meta-analysis has demonstrated that LVEDVI increased significantly after TC PVR but not surgical PVR and that LVESVI does not change after TC or surgical PVR.[17] A more recent small study showed an increase in

LVEDVI in both TC and surgical patients.[44] We were not able to demonstrate an improvement in LVEF in either the TC or hybrid cohort as others have done.[45,46]

Although we found tricuspid valve E/A ratios increased and mitral valve E/A ratios decreased after PVR our finding was not statistically significant. Frigiola and colleagues [47] demonstrated significant increases in tricuspid E/A ratios and decreases in mitral valve E/A ratios after surgical PVR. The significance of these findings in terms of diastolic dysfunction has not been fully elucidated.

ECG and Arrhythmia Outcomes

Arrhythmias are a significant problem in tetralogy of Fallot with increased risk for ventricular tachycardia, ventricular fibrillation, atrial flutter and atrial fibrillation.[48] We did not find a significant difference in any of the ECG parameters (PR interval, QRS duration, and QTc interval) after PVR. Others have found a reduction on QRS duration in surgical PVR [49] but not with TC PVR [50]. However, the surgical studies often included patients who had concomitant arrhythmia procedures performed which may have influenced the results. Two studies have found a shortening of the QTc interval with TC PVR [51] and TC PVR specifically for pulmonary regurgitation. [52] There are no other studies of arrhythmia changes after hybrid PVR.

There was no change in arrhythmias pre- and post-PVR for either TC or hybrid PVR. Others have documented a decrease in premature ventricular contractions in patients after PVR. [51] Advocates for surgical PVR argue that it allows concomitant arrhythmia treatment strategies. However, results for catheter ablation of ventricular tachycardia in tetralogy of Fallot patients have been improving with a recent study demonstrating an 82% success rate.[53]

Cardiopulmonary Exercise and NYHA Functional Class Outcomes

No significant changes were found in cardiopulmonary exercise parameters after PVR. Our peak oxygen consumption values were consistent with repaired tetralogy of Fallot in the literature. [54] Peak oxygen consumption has not been reported to improve after surgical PVR [55-58]. Results after TC PVR have shown mixed results with some studies showing improvement[59-61], particularly when TC PVR has been performed for obstructive right ventricle-pulmonary artery conduits,[62] or in patients with predominant pulmonic stenosis. [63] One study found small but significant improvements in the ratio of minute ventilation to carbon dioxide production at anaerobic threshold (a parameter not assessed in this study).[64] There were no previous reports of cardiopulmonary exercise testing in hybrid PVR.

NYHA functional class significantly improved in the TC PVR group but not the hybrid group. Others have found a similar improvement in NYHA functional class after TC PVR. There are only anecdotal case reports of NYHA functional class improvement after hybrid PVR. NYHA functional class improvements after surgical PVR has been well demonstrated.[65-71]

Symptom Outcomes

Symptoms of dyspnea and exercise intolerance improved in the entire group after PVR, but no differences were seen when examined by TC or hybrid procedure type. There are no other known studies that report specific symptoms before and after TC or hybrid PVR. Some studies used NYHA as a surrogate for symptoms. One surgical PVR study reported a reduction in fatigue, dyspnea, palpitations, syncope, ankle edema, and chest pain but paradoxically the number of subjects reporting an increase in job limitations doubled.[65]

HROQOL Outcomes

Due to the late introduction of HRQOL measures in our clinical protocol, the results are limited. There was no worsening in perceived physical appearance which reflects the lack of incision or a minimally invasive incision in most hybrid patients. It was encouraging that there were improvements in all of the subscales except Treatment II and Communication, though not statistically significant. Being able to use one tool across all ages with a specific cardiac module was an advantage. Only one study examining HRQOL in TC PVR could be found, showing positive improvements post-PVR.[61] There are no known studies reporting HRQOL in hybrid PVR. HRQOL has been reported to increase after surgical PVR with increases in physical functioning [72], mental health but not physical functioning [73], or with both mental and physical increasing on the SF-36. [74-76]

Costs

The higher costs for TC and hybrid PVR compared to surgical PVR reflect higher prices for the TC valves, the stents used, and for hybrid PVR, other devices such as vascular plugs used to remodel the right ventricular outflow tract. Data from Seattle [77] and the Pediatric Health Information Systems Database from 2011-2013[78] found the costs of TC PVR to be slightly higher than surgical PVR but not significantly so. Gatlin and co-authors[79] found device costs to be higher for TC PVR but total procedural costs were nearly identical. Another study found TC PVR costs to be significantly lower than surgical PVR[80] although TC PVR patients in this study did not spend any time in an intensive care unit, which is different from other studies. Our costs included procedures through 2017 and many of our procedures were in adults. All patients stayed in the intensive care unit until

discharge. These factors may account for some of the cost differences in our cohort. Although costs are higher for TC and hybrid procedures the recovery time is much shorter than for surgical PVR and enables individuals to go back to work/school quicker. The TC and hybrid PVR procedures may ultimately have fewer costs to society such as disability expenses.[80] However, the longevity of the procedures will also have to be factored into costs decisions and with TC and hybrid PVR being newer treatment modalities, the ultimate costs will not likely be known for years.

Study Limitations

This study was conducted at a single center with a small sample size (especially the number of paired pre-PVR and post-PVR tests) and with follow-up that was complete in only about 70% of patients that limited generalizability and statistical power to detect differences between the types of PVR approaches on outcomes. The CSMC program had a unique approach: to attempt a TC PVR approach first, then a hybrid PVR approach, and surgical PVR only if the other two approaches failed which also limits generalizability. There were also a variety of TC and hybrid PVR approaches used. The small sample size limited sub-analyses. Follow-up time was short with a median of 8.9 months for the TC patients and 11.9 months for the hybrid patients. The amount of HRQOL data was also limited due to the late introduction of HRQOL instruments into the clinical protocol. The cohort was largely White and non-Hispanic, which limits generalization to other races/ethnic groups.

Conclusion

As the use of less invasive PVR becomes more common, it is important to assess the outcomes from TC and hybrid PVR to educate future patient/families about procedural risks and benefits. This study demonstrated that hybrid PVR can be performed with similar functional and volumetric outcomes to TC PVR. The median 2-day length of stay and a slightly higher mortality rate and cost are noted, however statistical significance is lacking in the hybrid PVR outcomes due to small sample sizes available to date. Outcomes for TC and surgical PVR were similar in terms of heart remodeling but length of stay, mortality, and significant complications are higher with surgical PVR. Earlier referral of individuals with genetic syndromes/developmental delay is advocated to improve non-invasive PVR and HRQOL in this group. Further investigation into HRQOL in the TC and hybrid groups is needed. Further follow-up with larger sample sizes in both native outflow tract TC PVR and hybrid PVR will be needed to ascertain longer-term outcomes. Although findings from this study cannot be used to inform choices for individual

patients, the initial knowledge of the outcomes for these procedures can be used to educate the health care professional how to advise specific patients about the different PVR choices.

Funding: This work was supported by a Robert Wood Johnson/Cedars-Sinai Medical Center Future of Nursing Scholar award to Marion McRae.

Conflicts of Interest: Dr. Zahn is a proctor/consultant for Edwards Life Sciences and Medtronic. The remainder of the authors have no conflicts of interest to disclose.

Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Table 1

Subject Demographics and Clinical Variables

Parameter	Transcatheter (n=32)	Hybrid (n=15)
Age at current PVR in years (range)	24.5 (6.0-72.0)	23.0 (5.0-62.0)
Male sex (%)	20 (62.5)	7 (46.7)
Ethnicity:		
Non-Hispanic or Latino (%)	25 (78.1)	10 (66.7)
Race (%)		
White	27 (84.4)	13 (86.7)
Black	2 (6.3)	0 (0.0)
Indian/Alaskan Native	1 (3.1)	0 (0.0)
Asian	2 (6.3)	2 (13.3)
Hawaiian Islander/Pacific Islander	0 (0.0)	0 (0.0)
Genetic syndrome (%)	7 (21.9)	3 (20.0)
Age at palliative procedure in years (range)	0.08 (0.0-1.8)	1.2 (0.01-2.0)
Age at reparative surgery in years (range)	2 (0.0-46.0)	1.0 (0.2-22.0)
Type of reparative surgery (%)		
TOF repair transannular patch	16 (50.0)	11 (77.3)
TOF repair valve-sparing	0 (0.0)	1 (6.7)
TOF repair with pulmonary arterioplasty	1 (3.1)	0 (0.0)
Pulmonary valvotomy	1 (3.1)	2 (13.3)
Pulmonary valvuloplasty	1 (3.1)	0 (0.0)
Right ventricle to pulmonary artery conduit	3 (9.4)	0 (0.0)
Other	9 (28.1)	1 (6.7)
Unknown	1 (3.1)	0 (0.0)
Previous PVR (%)	16 (50.0)	0 (0.0)
Primary physiology prior to PVR (%)		
Pulmonary regurgitation	19 (59.4)	14 (93.3)
Pulmonary stenosis	13 (40.6)	1 (6.7)
Permanent pacemaker pre-PVR (%)	3 (9.4)	2 (13.3)
ICD pre-PVR (%)	3 (9.4)	1 (6.67)

Legend: ICD=internal cardioverter defibrillator; PVR=pulmonary valve replacement; TOF=tetralogy of Fallot

Table 2

Pulmonary Valve Procedural Variables and Procedural Outcomes

Parameter	Transcatheter (n=32)	Hybrid (n=15)
Weight in kg (SD)	60.1 (24.7)	71.5 (25.1)
Body mass index (range)	21.2 (13.7-33.7)	25.1 (13.8-40.7)
Unsuccessful implant (%)	3 (9.4)	1 (6.7)
Pre-stenting (%)	27 (84.4)	14 (93.3)
Valve type (%)		
Medtronic Melody	12 (37.5)	2 (13.3)
Edwards Sapien XT	9 (28.1)	10 (66.7)
Edwards Sapien S3	8 (25.0)	3((20.0)
None	3 (9.4)	0 (0.0)
Valve size at final expansion (range)	23 (16-29)	29 (18-29)
First valve success (%)	30 (93.8)	14 (93.3)
Number of annular remodeling devices used (range)	n/a	2 (1-5)
Coronary compression (%)	0 (0.0)	0 (0.0)
Aortic compression (%)	1 (3.1)	0 (0.0)
Procedural time in minutes (SD)	228.3 (68.6)	310.3 (68.9)
Fluoroscopy time in minutes (range)	42.4 (16.6-240.0)	39.2 (19.3-85.4)
Radiation exposure in mGy (SD)	1677.1 (1246.1)	2431.2 (1688.8)
Arrhythmias during implant (%)	0 (0.0)	1 (6.7)
Groin bleeding (%)	3 (9.4)	0 (0.0)
Vascular complication (%)	3 (9.4)	9 (0.0)
Wire perforation (%)	1 (3.1)	0 (0.0)
Dissection (contained) (%)	2 (6.3)	0 (0.0)
Blood transfusion (%)	2 (6.3)	2 (13.3)
Pericardial effusion (%)	0 (0.0)	1 (6.7)
Access site infection (minor) (%)	0 (0.0)	2 (13.3)
Pneumothorax (%)	0 (0.0)	2 (13.3)
Hypotension (%)	0 (0.0)	1 (6.7)
Stent or valve migration (%)	1 (3.1)-stent	1 (6.7)-stent and valve
Acute kidney injury (%)	1 (3.1)	1 (6.7)
Contrast reaction (%)	2 (6.3)	0 (0.0))
Nerve injury (%)	0 (0.0)	1 (6.7)
Tricuspid valve chordal rupture (%)	0 (0.0)	3 (20.0)
Chronic pain syndrome (%)	0 (0.0)	1 (6.7)
Length of stay in days (range)	1.0 (1.0-33.0)	2.0 (1.0-91.0)
30-day mortality (%)	1 (3.1)	1 (6.7)

Legend: mGy= milligray; SD=standard deviation

Table 3

Mid-Term Outcomes of Transcatheter and Hybrid Pulmonary Valve Replacements

Parameter	Transcatheter (n=32)	Hybrid (n=15)
Follow-up time in days (range)	266 (4-1256)	356.5 (3-1239)
Follow-up complete (%)	22 (68.8)	11 (73.3)
Reasons for lack of follow-up (%)		
Insurance	6 (18.8)	0 (0)
Distance	3 (9.4)	1 (6.7)
Followed by outside cardiologist who did not share follow-up information	1 (3.1)	2 (13.3)
Unknown	0 (0.0)	1 (6.7)
Stent fracture (%)	1 (3.1)	0 (0.0)
Infective endocarditis (%)	0 (0.0)	0 (0.0)
Structural valve deterioration (%)	1 (3.1)	0 (0.0)
Repeat PVR during study period (%)	2 (6.3)	0 (0.0)
All-cause mortality during study period (%)	1 (3.1)	2 (13.3)

Legend: PVR=pulmonary valve replacement

Table 4

Paired Pre- and Post-Pulmonary Valve Replacement Cardiac MRI/MRA Outcomes

Transcatheter:							
Parameter	**Pre-PVR median (Range)**	**Post-PVR median (Range)**	**Num-ber of paired results**	**Wilcoxon test statistic (T)**	**Standard-ized test statistic (z)**	**SE**	**p value**
RVEDVI (mL/m^2)	142.5 (118.0-166.9)	105.0 (90.4-139.5)	7	2.000	-2.028	5.92	0.043
RVESVI (mL/m^2)	75.1 (53.1-95.0)	46.6 (39.2-78.3)	6	0.000	-2.201	4.77	0.028
RVEF (%)	46.6 (23.0-62.7)	53.59 (43.8-59.6)	8	29.000	1.540	7.14	0.123
Pulmonary valve RF (%)	37.5 (25.0-42.0)	2.0 (0.0-11.0)0	6	0.000	-2.201	4.77	0.028
LVEDVI (mL/m^2)	82.9 (54.2-127.7)	89.5 (58.5-99.5)	9	27.000	0.533	8.44	0.594
LVESVI (mL/m^2)	37.4 (16.0-57.1)	38.3 (28.8-53.6)	7	14.000	0.000	5.92	1.000
LVEF (%)	56.7 (41.0-75.0)	57.4 (54.2-66.6)	8	19.000	0.140	7.14	0.889
Hybrid:							
RVEDVI (mL/m^2)	166.0 (100.8-198.2)	120.9 (75.0-124.1)	5	0.000	-2.023	3.71	0.043
RVESVI (mL/m^2)	78.5 (46.3-102.8)	45.0 (38.0-70.3)	3	0.000	-1.604	1.87	*
RVEF (%)	49.9 (23.0 -54.1)	51.3 (40.0-58.2)	5	8.000	0.135	3.71	*
RF (%)	46.0 (35.0-50.0)	2.0 (0.0-7.0)	3	0.000	-1.604	1.87	*
LVEDVI (mL/m^2)	77.1 (36.0-90.0)	85.2 (62.0-98.3)	5	10.000	0.674	3.71	*
LVESVI (mL/m^2)	31.0 (24.9-33.5)	31.0 (24.9-33.5)	3	5.000	1.069	1.87	*
LVEF (%)	57.9 (40.0-61.6)	59.6 (52.8-69.6)	4	6.000	0.365	2.73	*

*=no p values reported due to small sample size

Legend: LVEDVI =left ventricular end-diastolic volume index; LVEF=left ventricular ejection fraction; LVESVI=left ventricular end-systolic volume index; MRA=magnetic resonance angiography; MRI=magnetic resonance imaging; RF=regurgitant fraction; RVEDVI=right ventricular end-diastolic volume index; RVEF=right ventricular ejection fraction; RVESVI=right ventricular end-systolic volume index; SE=standard error.

Table 5

Paired Pre- and Post-Pulmonary Valve Replacement Echocardiography Outcomes

Transcatheter:							
Parameter	**Pre-PVR median (Range)**	**Post-PVR median (Range)**	**Number of pairs**	**Wilcoxon test statistic (T)**	**Standardized test statistic (z)**	**SE**	**P value**
RVEF[1] (qualitative)	1 (1-4)	1 (1-4)	22	0.000	-2.121	3.54	0.03
PR[2]	5 (1-5)	1 (1-5)	27	17.000	-3.837	34.66	0.00
TR[2]	2 (1-5)	3 (1-5)	27	63.000	1.275	13.73	0.20
LVEDVI (mL/m^2)	82.9 (54.2-127.7)	89.5 (58.5-99.5)	15	102.000	2.385	17.61	0.02
LVESVI (mL/m^2)	37.4 (16.0-57.1)	38.3 (28.8-53.6)	14	56.000	0.220	15.93	0.83
LVEF (%)	56.7 (41.0-75.0)	57.4 (54.2-66.6)	22	183.000	1.834	30.80	0.07
Pulmonary valve PG (mmHg)	17.8 (2.5-52.4)	26.7 (5.0-132.0)	23	80.000	-1.764	32.88	0.08
Pulmonary valve MG (mmHg)	20.0 (0.0-17.0)	14.5 (6.0-28.0)	14	22.500	-1.608	14.31	0.11
MV E:A ratio	1.8 (1.0-2.5)	1.55 (0.7-2.7)	8	9.000	-1.276	7.05	0.20
TV E:A ratio	1.5 (1.2-1.8)	1.7 (1.1-2.0)	3	3.000	0.000	1.84	*
Hybrid:							
RVEF[1]	1 (1-4)	1 (1-4)	11	-0.935	0.935	6.96	0.35
PR[2]	5 (4-5)	2 (1-4)	15	-3.449	-3.449	17.40	0.00
TR[2]	3 (1-4)	3 (2-5)	15	1.155	1.155	7.79	0.25
LVEDVI (mL/m^2)	62.9 (25.4-189.3)	70.1 (46.5-231.3)	8	1.680	1.680	7.14	0.09
LVESVI (mL/m^2)	25.2 (16.4-118.4)	22.8 (16.4-118.4)	7	0.338	0.338	5.92	0.74
LVEF (%)	59.0 (41.5-65.0)	55.5 (44.4-71.7)	11	-0.622	-0.622	11.25	0.53
Pulmonary valve PG (mmHg)	13.6 (0-30.0)	15.2 (7.3-28.0)	12	1.177	1.177	12.75	0.24
Pulmonary valve MG - (mmHg)	9 (0-12.0)	9.0 (0-16.0)	7	0.944	0.944	3.71	0.35
MV E:A ratio	2.3 (0.9-3.4)	1.45 (1.4-1.1)	6	-1.807	-1.807	4.70	0.07
TV E:A ratio	0.9 (0.6-1.7)	1.3 (1.2-1.8)	3	0.535	0.535	1.87	*

*no p values reported due to small sample size

[1]RVEF qualitative score: 1=normal function, 2=mildly depressed function, 3=moderately depressed function, 4=severely depressed function

[2] Regurgitation score: 1=none, 2=trace, 3=mild, 4=moderate, 5=severe

Legend: LVEDVI=left ventricular end-diastolic volume index; LVEF=left ventricular ejection fraction; LVESVI=left ventricular end-systolic volume index; MG=mean gradient; MV=mitral valve; PG=peak gradient; PR=pulmonary regurgitation; PVR=pulmonary valve replacement; RVEF=right ventricular ejection fraction; SE=standard error; TR=tricuspid regurgitation; TV=tricuspid valve

Table 6

Paired Pre- and Post-Pulmonary Valve Replacement Electrocardiogram Results

Parameter	Pre-PVR mean ± SD	Post-PVR mean ± SD	Mean differ-ence	t-test statistic	df	p value	95% CI (lower, upper)
Transcatheter:							
PR interval	162.7 ± 30.0	160.4 ± 33.7	2.30	0.497	19	0.63	-7.39, 11.99
QRS duration	127.4 ± 36.5	127.4 ± 38.5	0.00	0.000	20	1.00	-3.8, 3.87
QTc duration	458.7 ± 41.3	454.3 ± 38.2	4.44	0.747	20	0.46	-7.94, 16.80
Hybrid:							
PR interval	161.3 ± 33.6	164.4 ± 33.4	-3.14	-0.728	13	0.48	-12.47, 6.18
QRS duration	152.7 ± 16.5	148.3 ± 14.0	4.43	1.414	13	0.18	-2.34,11.20
QTc duration	470.0 ± 16.7	468.2 ± 23.3	1.85	0.237	12	0.82	-15.14, 18.84

Legend: CI=confidence interval; df=degrees of freedom; PVR=pulmonary valve replacement, SD=standard deviation

Table 7

Paired Pre- and Post-Pulmonary Valve Replacement Arrhythmia Outcomes (Whole Group)

Holter/Zio patch Parameter	Pre-PVR median (range)	Post-PVR median (range)	Number of pairs	Wilcoxon test statistic (T)	Standardized test statistic (Z)	SE	p value
Low HR	50 (35-64)	45.5 (35-54)	9	13.000	-1.126	8.434	0.26
Average HR	72 (51-91)	72.5 (61-105)	8	16.00	0.339	5.895	0.73
Maximum HR	140 (97-185)	162 (106-214)	10	26.500	0.474	8.434	0.64
Heart Block[1]	0 (0-1)	0 (0-2)	9	2.000	0.447	1.118	0.65
PAC[2]	1 (0-3)	1 (0-3)	10	5.000	-0.687	3.640	0.49
PVC[2]	1 (0-2)	1 (0-3)	8	3.000	0.000	1.837	1.00
	Number with parameter pre-PVR (%)	**Number with parameter post-PVR (%)**	**Number of paired results**	**McNemar test statistic**	**df**	**p value**	
SVT	2 (22.2)	2 (22.2)	9	0.000	1	1.00	
Bigeminy	1 (11.1)	0 (0.0)	9	0.000	1	1.00	
Trigeminy	0 (0.0)	0 (0.0)	8	0.000	1	1.00	
VT	1 (12.5)	0 (0.0)	8	0.000	1	1.00	

[1]Heart Block: 0=none;1=first degree, 2=second degree Type I, 3=second degree Type II, 4=third degree
[2]Frequency scale: 0=none; 1=rare, 2=occasional, 3=frequent

Legend: df=degrees of freedom; HR=heart rate; PAC-premature atrial contraction; PVC=premature ventricular contraction; PVR=pulmonary valve replacement; SE=standard error; SVT=supraventricular tachycardia; VT=ventricular tachycardia.

Table 8

Paired Pre- and Post-Pulmonary Valve Replacement Cardiopulmonary Exercise Test Outcomes

Parameter	Pre-PVR median (range)	Post-PVR median (range)	Number of paired results	Wilcoxon test statistic (T)	Standardized test statistic (z)	SE	p value
Transcatheter:							
VO2 max (mL/min/kg)	22.3 (9.7-31.5)	22.5 (14.0-32.0)	3	3.000	0.000	1.87	*
Oxygen pulse at rest (mL/beat)	4.1 (3.0-4.6)	3.5 (2.0-6.0)	2	3.000	1.342	1.12	*
Oxygen pulse peak (mL/beat)	10.5 (8.0-17.4)	10.0 (6.0-11.0)	3	4.500	0.816	1.84	*
Hybrid:							
VO2 max (mL/min/kg)	20.4 (15.6-55.0)	28.0 (26.0-32.0)	2	3.000	1.342	1.11	*
Oxygen pulse at rest (mL/beat)	4.4	5.5	1	0.000	-1.000	0.50	*
Oxygen pulse peak (mL/beat)	13.4	19.0	1	0.000	-1.000	0.50	*

*no p values reported due to small sample size

Legend: PVR=pulmonary valve replacement; SE=standard error; VO2=oxygen consumption

Table 9

Paired Pre- and Post-Pulmonary Valve Replacement New York Heart Association Functional Class Outcomes

Pre-PVR NYHA Class median (range)	Post-PVR NYHA Class median (range)	Number of pairs	Wilcoxon test statistic (T)	Standardized test statistic (z)	SE	p value
Transcatheter:						
2 (1-4)	1 (1-4)	29	16.000	-2.892	17.44	0.00
Hybrid:						
2 (1-4)	1 (1-4)	15	7.000	-1.613	6.82	0.11

Legend: NYHA=New York Heart Association; PVR=pulmonary valve replacement; SE=standard error

Table 10

Paired Pre- and Post-Pulmonary Valve Replacement Self-Reported Symptom Outcomes

Symptom	Number of patients with symptom pre-PVR (%)	Number of patients with symptom post-PVR (%)	Num-ber of pairs	McNemar test statistic	df	p value
Transcatheter:						
Dyspnea on exertion	14 (48.3)	7 (24.1)	29	3.273	1	0.07
Palpitations	9 (32.1)	8 (28.6)	28	0.000	1	1.00
Chest pain	4 (20.0)	3 (15.0)	20	0.000	1	1.00
Orthopnea	1 (3.6)	2 (7.1)	28	0.000	1	1.00
Ankle edema	3 (11.5)	2 (7.7)	26	0.000	1	1.00
Presyncope	6 (25.0)	3 (12.5)	24	0.444	1	0.51
Syncope	5 (17.2)	2 (6.9)	29	1.333	1	0.25
Fatigue	11 (39.3)	8 (28.6)	28	0.267	1	0.61
Exercise intolerance	11 (39.3)	5 (17.9)	28	2.083	1	0.15
Anxiety	5 (17.9)	5 (17.9)	29	0.000	1	1.00
Depression	0 (0.0)	0 (0.0)	31	0.000	1	1.00
Hybrid:						
Dyspnea on exertion	8 (53.3)	5 (33.3)	15	1.333	1	0.25
Palpitations	5 (35.7)	3 (21.4)	14	0.167	1	0.69
Chest pain	2 (18.2)	2 (18.2)	11	0.000	1	1.00
Orthopnea	2 (14.3)	0 (0.0)	14	0.500	1	0.50
Ankle edema	3 (20.0)	2 (13.3)	15	0.000	1	1.00
Presyncope	4 (28.6)	2 (14.3)	14	0.167	1	0.69
Syncope	5 (33.3)	4 (26.7)	15	0.000	1	1.00
Fatigue	5 (33.3)	3 (20.0)	15	0.125	1	0.73
Exercise intolerance	7 (46.7)	2 (13.3)	15	2.286	1	0.13
Anxiety	3 (20.0)	2 (13.3)	15	0.000	1	1.00
Depression	1 (6.7)	1 (6.7)	15	0.000	1	1.00

Legend: df=degrees of freedom; PVR=pulmonary valve replacement.

Table 11

Paired Pre- and Post-Pulmonary Valve Replacement PedsQL Generic and Cardiac Module Outcomes (Whole Group)

Scale/Subscale	Pre-PVR median score (range)	Post-PVR median score (range)	Number of paired results	Wilcoxon test statistic (T)	Standardized test statistic (z)	SE	P value
PedsQL Generic Scale:							
Physical Scale	60.0 (19-88)	73.0 (47-91)	6	19.500	1.892	4.76	0.06
Psychological Scale	71.0 (27-100)	87.5 (35-95)	6	14.000	1.761	3.69	0.08
Total Score	66.0 (32-100)	85.0 (39-100)	6	14.000	1.753	3.71	0.08
PedsQL Cardiac Module:							
Health problems and treatment	61.0 (54-100)	79.0 (57-100)	5	9.000	1.473	2.72	*
Treatment II	90.0 (80-100)	90.0 (89-95)	2	1.500	0.000	1.06	*
Perceived physical appearance	75.0 (50-100)	100.0 (50-100)	5	3.000	1.414	1.06	*
Treatment anxiety	75.0 (25-100)	100.0 (25-100)	5	6.000	1.604	1.87	*
Cognitive problems	65.0 (60-100)	85.0 (25-95)	5	7.000	-0.136	3.67	*
Communication	83.0 (0-100)	83.0 (0-100)	5	3.000	0.000	1.87	*

*no p values reported due to small sample size

Legend: PVR=pulmonary valve replacement; SE=standard error

Summary

This dissertation explored use of the Omaha System to develop new connections between variables in an existing large data set. It allowed me to build skill in handling large data sets, extracting, and categorizing variables in preparation for the final dissertation study. The dissertation also explored outcomes from three types of pulmonary valve replacement (PVR) used in the treatment of pulmonary regurgitation and stenosis in congenital heart disease with the purpose of building knowledge to inform health care providers who need to educate patients/families about these procedures. One manuscript on this topic examined the state of the literature and allowed me to gain experience with meta-analysis. The final manuscript allowed me to apply the skills learned in a study of PVR outcomes.

Manuscript Contributions to Answering the Overarching Question

The quasi-meta-analysis (Manuscript I) identified gaps related to knowledge about PVR. These included a lack of: post-procedural outcomes for hybrid PVR, outcome measures at least one year post-PVR, and paired pre-post PVR measures. There were few measures of diastolic heart function, and limited outcomes for symptoms, arrhythmias, exercise capacity, and health-related quality of life (HRQOL) for either TC or hybrid PVR.

Manuscript II demonstrated that theoretical frameworks such as the Omaha System can be used to transform large datasets into variables that can then be subjected to visualization techniques to help ascertain new relationships among variables in the data base. Key findings in the multivariate model obtained from the study were that subjects

who scored better on the mental health behavior scale and the neuro-musculo-skeletal function scale were less likely to develop new venous leg ulcers with an area under the curve of c=0.758. Additionally, individuals at risk of developing, or those who have had an ulcer in the past were more likely to adhere to treatment and less likely to develop a new ulcer when they expressed confidence in their ability to manage symptoms. These variables were previously non-mapped concepts for relevance to venous disease and will inform the design of future studies. This manuscript demonstrated that it is possible to apply nursing theory to large databases to investigate new relationships that would benefit from future study. These skills will be needed to work with large congenital heart disease databases and data from electronic health records.

Findings from the PVR study (Manuscript III) suggest that preliminary outcomes for hybrid PVR had similar functional and volumetric outcomes as TC PVR with a slightly higher mortality rate and cost however lack of statistical significance may have been due to small sample size. Outcomes for TC and surgical PVR were similar in terms of heart remodeling but length of stay, mortality, and major complications appear to be higher for surgical PVR. All deaths after TC and hybrid PVR occurred in individuals with genetic syndromes/developmental delay highlighting the need for earlier referral and better understanding of management of these patients to achieve successful outcomes.

Limitations of the Dissertation Research and Lessons Learned

There are several limitations of Manuscript I of the quasi-meta-analyses of TC and surgical pulmonary valve replacement outcomes. The review included only one randomized controlled trial. Most of the studies were observational cohorts, many of

which were retrospective which limits causal generalization. Heterogeneity of the study populations led to analysis difficulties in comparing outcomes between patients with pulmonary regurgitation and pulmonary stenosis. There were too few outcomes from hybrid PVR, which can take many forms, to examine at the time of the analysis. The review was conducted by a single author which may have introduced selection bias. The funnel plots from the study demonstrated possible publication bias. Therefore, studies with non-significant results or small studies may have been underreported which can bias the results.

The limitation of the work in Manuscript II was that a congenital heart disease data could not be used for this manuscript due to the lack of availability suitable database.

Limitations of the TC and hybrid PVR study (Manuscript III) include that Cedars-Sinai Medical Center where the study was conducted had a novel approach to attempt TC PVR first on all patients, and if this failed, attempt hybrid PVR, and only if this failed, attempt surgical PVR, all under one anesthetic if the patient/family desired this. This policy limits generalizability of the results as few other centers have a similar approach. As a consequence of this policy, too few surgical PVR to be included in the analysis were conducted at this center. Therefore, comparisons of TC and hybrid PVR were made to surgical PVR reported in the literature and results from the quasi-meta-analysis presented in Manuscript I. The sample size in this study was small, particularly in the hybrid PVR group, which limited statistical analysis and generalizability of the findings. As well, there were a variety of TC and hybrid approaches used in this study but, due to the small sample size, sub-analyses could not be performed.

Importance of the Theory/Model to Guide Findings

The Wilson and Cleary conceptual model of health-related quality of life (HRQOL) (12) provided the framework in which variables were conceptualized and examined in patients with pulmonary regurgitation and stenosis requiring PVR. Relationships among these variables were established to determine the impact of HRQOL which guided the quasi-meta-analysis (Manuscript I). The framework was also used in the study evaluating outcomes after TC and hybrid PVR in a single center (Manuscript III). It was used to guide selection and categorization of variables collected from the electronic health record.

The Omaha System was a useful method to guide the categorization of variables from a variety of demographic, physical, psychological and physiological data and scales into the physiological domain, health-related behaviors domain, or the psychosocial domain. The model was used to examine relationships within the dataset with mental behavior being a predictor of adherence to the study protocol. Relationships within the Omaha System dataset at baseline were analyzed to predict ulcer development. The Omaha System could potentially be used with CHD databases.

Research Trajectory

Next steps after this dissertation include continued follow-up of PVR outcomes to inform my ongoing practice. I would like to gain further experience in building prospective databases that can help answer the questions that need to be addressed in congenital heart disease. I would also like to further investigate the impact of genetic syndrome on outcomes as there are many genetic syndromes seen in patients undergoing

PVR and, as we demonstrated, in manuscript III, outcomes were poorer in this group. Understanding why these poor outcomes occur and what interventions would improve outcomes will be important going forward.

I would also like to gain more experience building on the work of manuscript II in working with large data sets to investigate clinical congenital heart disease outcomes and factors influencing outcomes. This is important in congenital heart disease as larger sample sizes are needed than most centers have patients to conduct trials.

Contribution of this Research to Health, Nursing, Interprofessional Sciences, and Clinical Care

Dissemination of findings from the meta-analysis and secondary data analysis will occur through publications (two of the manuscripts have either been published or are accepted for publication) and at professional meetings. The results of Manuscript II have also appeared on a poster, for which I am first author, presented at Midwestern Nurses Research Society in April 2017. The overall intent of the body of work associated with this dissertation is to inform health care providers about the advantages, disadvantages, and outcomes of PVR for pulmonary regurgitation and pulmonary stenosis. Taking the data from this study, along with future studies with larger sample sizes, begins to build the knowledge that interprofessional teams need to educate patients/families about the potential treatment options. This is important to clinical care as it may direct patients/families to the most appropriate PVR technique given their anatomy, physiology, risk factors, and preferences. I hope that it encourages health care providers to refer these

patients earlier when there are more treatment options to preserve functional status and health-related quality of life.

There is a tremendous amount of data being collected in electronic health records every day by nurses, nurse scientists, and practitioners who conduct clinical research and related quality improvement projects. These rich data sources are rarely accessed in the aggregate, with a common taxonomy to inform new models of care or to uncover hidden relationships that could provide new insights for generation of hypotheses. The work using the Omaha system highlights how nurses can use a model such as this to "mine" large datasets such as electronic health records and research data sets to explore relationships among variables that may prompt further nursing research.

Appendix I

INSTITUTIONAL REVIEW BOARD APPROVAL CEDARS-SINAI MEDICAL CENTER

CEDARS-SINAI

Full AAHRPP Accreditation

Office of Research Compliance and Quality Improvement, 6500 Wilshire Blvd., Suite 1800, Los Angeles, CA 90048

3/6/2017

To: EVAN ZAHN
CC: MARION McRAE
From: Stephen Lim, M.D. Executive Chairperson
On Behalf of the CSMC Institutional Review Boards
Subject: IRB Approval for Ame00019555

Please note that the Cedars-Sinai Institutional Review Board (CSMC IRB) has approved the modification to the STUDY summarized below:

IRB No.:	Ame00019555 /Pro00047065
Study Title:	An exploratory study of hemodynamic, symptom, functional, and health-related quality of life outcomes after transcatheter and hybrid pulmonary valve replacement versus surgical pulmonary valve replacement.
Amendment Title:	Amendment #1
Date of Approval:	**3/6/2017** Approved via Expedited Review
Study Expiration Date:	**11/30/2017**
IRB Review Date:	3/6/2017
Principal Investigator:	EVAN ZAHN
Co-Investigators:	MARION McRAE
Other Study Staff:	VEENA SIVARAJAN BERNICE COLEMAN MARION McRAE
Summary of Modifications:	Changes in Personnel Participation of Non-CSMC sites Protocol, including modifications to study procedures
CSMC Federalwide Assurance No.:	FWA 00000468

CEDARS-SINAI

Office of Research Compliance and Quality Improvement, 6500 Wilshire Blvd., Suite 1800, Los Angeles, CA 90048

1/6/2017

To: EVAN ZAHN
CC: MARION McRAE
From: Stephen Lim, M.D. Executive Chairperson
On Behalf of the CSMC Institutional Review Boards
Subject: IRB Approval for Pro00047065

Please note that the Cedars-Sinai Institutional Review Board (CSMC IRB) has approved you to conduct research involving human subjects. Please review the following information summarizing the approval granted:

IRB No.:	Pro00047065
Study Title:	An exploratory study of hemodynamic, symptom, functional, and health-related quality of life outcomes after transcatheter and hybrid pulmonary valve replacement versus surgical pulmonary valve replacement.
Approval Period:	**1/6/2017 through 11/30/2017**
	Approved via Expedited Review Category 5
IRB Review Date:	12/30/2016
Principal Investigator:	EVAN ZAHN
Co-Investigators:	MARION McRAE
Other Study Staff:	BERNICE COLEMAN MARION McRAE
CSMC Federalwide Assurance No.:	FWA 00000468
Funding Information:	Internal CSMC Funding /

Please review this checklist for guidance on maintaining confidentiality and security of data accessed and/or abstracted for research: **Confidentiality Checklist**

Appendix II

INSTITUTIONAL REVIEW BOARD APPROVAL MEDICAL UNIVERSITY OF SOUTH CAROLINA

MUSC
MEDICAL UNIVERSITY
of SOUTH CAROLINA

Institutional Review Board for Human Research (IRB)
Office of Research Integrity (ORI)
Medical University of South Carolina

Harborview Office Tower
19 Hagood Ave., Suite 601, MSC857
Charleston, SC 29425-8570
Federal Wide Assurance # 1888

Pro00063374

"An exploratory study of hemodynamic, symptom, functional, and health-related quality of life outcomes after transcatheter and hybrid pulmonary valve replacement versus surgical pulmonary valve replacement"

Submitted by: Marion McRae
Department: College of Nursing

Type: **Facilitated Review**
Facilitated Review Date: 2/27/2017

The MUSC IRB agreed to rely on Cedars-Sinai IRB for the review and continuing oversight for its human subjects research for this study.

Stacey Goretzka, CIP
IRB Manager, **Medical University of South Carolina**

***Electronic Signature**: *This document has been electronically signed by the reviewer through the HSSC eIRB Submission System.*

Appendix III

PERMISSION TO USE THE PEDSQL CORE SCALES AND MODULE IN CLINICAL FOLLOW-UP

User agreement
Special Terms

Mapi Research Trust, a non-for-profit organisation subject to the terms of the French law of 1st July 1901, registered in Carpentras under number 453 979 346, whose business address is 27 rue de la Villette, 69003 Lyon, France, hereafter referred to as "MRT" and the User, as defined herein, (each referred to singularly as a "Party" and/or collectively as the "Parties"), do hereby agree to the following User Agreement Special and General Terms:

MRT Contact:

Mapi Research Trust
PROVIDE
Address: 27 rue de la Villette, 69003 LYON, France
Telephone: +33 4 72 13 65 75
Fax: +334 72 13 66 82

RECITALS

The User acknowledges that it is subject to these Special Terms and to the General Terms of the Agreement, which are included in Appendix 1 to these Special Terms and fully incorporated herein by reference. Under the Agreement, the Questionnaire referenced herein is licensed, not sold, to the User by MRT for use only in accordance with the terms and conditions defined herein. MRT reserves all rights not expressly granted to the User.

The Parties, in these Special Terms, intend to detail the special conditions of their partnership.

The Parties intend that all capitalized terms in the Special Terms have the same definitions as those given in article 1 of the General Terms included in Appendix 1.
In this respect, the Parties have agreed as follows:

Article 1. CONDITIONS SPECIFIC TO THE USER

Section 1.01 Identification of the User

User Name : ***[complete the name of the individual or of the company]*** Marion E. McRae.....

Legal form : ***[individual or company's legal form]***.....

Address : ***[personal address or address of registered office]***Cedars-Sinai Medical Center, 127 South San Vicente Blvd., AHSP A3404, Los Angeles, CA.....

.....

.....

Country : USA.....

.....

Name of the contact in charge of the Agreement: Marion E. McRae.....

Telephone number: 310 423-1153.....Fax number: 310 423-6795 .....

Email address: marion.mcrae@cshs.org.....

If different:

Legal form : ***[individual or company's legal form]***.....

Address : ***[personal address or address of registered office]***.....

.....

.....

Country : .....

Billing address: as above .....

.....

.....

.....

VAT number (if applicable): .....

Addressee: .....

PO number or internal reference (if applicable): .....

Section 1.02 Identification of the Questionnaire

Title of the Questionnaire:	PedsQL™ (Pediatric Quality of Life Inventory™)
Author:	James W. Varni
Owner:	James W. Varni
Copyright notice	Copyright © 1998 JW Varni, Ph.D. All rights reserved.
References:	See Appendix 2

Article 2. RIGHTS TO USE

Section 2.01 Context of the Use of the Questionnaire

The User undertakes to only use the Questionnaire in the context of the Study as defined hereafter.
[Tick the box and complete the corresponding fields]

☐ *individual clinical practice (please go directly to section 2.02)*

Planned term of use: .....

Number of patients expected: .....

x☐ *clinical project or study*

Title:	Evaluation of pulmonary valve replacement outcomes .....
Study/protocol reference:	.....
Disease or condition:	Pulmonary valve replacement .....
Type of research:	☐ clinical trial : ☐ Phase II / ☐ Phase III
	x☐ epidemiologic/observational
	☐ other: .....
Questionnaire used as primary end point:	☐ yes
	x☐ no
Number of patients expected:	150.....
Number of submissions to the Questionnaire for each patient:	5 .....
Term of clinical follow-up for each patient:	5 years.....
Planned term for project:	start (month/year): June 2016.....
	end (month/year): June 2021 .....
Mode of Administration:	x☐ paper
	☐ electronic
If electronic administration, please indicate mode of data collection:	☐ Hand held device – specify device: .....
	☐ Interactive Voice Response (IVR) – specify: .....
	☐ Web - specify website: .....

☐ Digital Pen - specify device: .....

☐ Tablet - specify device: .....

Use of IT Company (e-vendor):

☐ other - specify: .....

☐ no

☐ yes – names of IT Company and contact:.....

☐ *other project*

Title: .....

Disease or condition: .....

Planned term of use: start (month/year): .....

end (month/year): .....

Description of the project: .....

.....

.....

Presentation format of project: .....

Requested module(s): *(please tick the appropriate box(es))*

PedsQL™ Generic Core Scales

Please specify: Standard ☐ Acute ☐ Both ☐

Adult (over 26)		Young Adult (18-25)		Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Self-report	Parent proxy-report	Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☐

PedsQL™ Infant Scales

Please specify: Standard ☐ Acute ☐ Both ☐

☐ Parent-report form (1-12 months) ☐ Parent-report form (13-24 months)

PedsQL™ Short Form 15 Generic Core Scales

Please specify: Standard ☐ Acute ☐ Both ☐

Adult (over 26)		Young Adult (18-25)		Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Self-report	Parent proxy-report	Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PedsQL™ Arthritis Module

Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐

PedsQL™ Asthma Module

Please specify: Standard ☐ Acute ☐ Both ☐

Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐

PedsQL™ Short Form 22 Asthma Module

Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐

PedsQL™ Brain Tumor Module

Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐

PedsQL™ Cardiac Module

Adult (over 26)		Young Adult (18-25)		Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Self-report	Parent proxy-report	Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☒☐	☐

PedsQL™ Cancer Module

Please specify: Standard ☐ Acute ☐ Both ☐

Adult (over 26)	Young Adult (18-25)		Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Self-report	Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

PedsQL™ Cerebral Palsy Module

Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐

PedsQL™ Cognitive Functioning Scale*

Please specify: Standard ☐ Acute ☐ Both ☐

Adult (over 26)		Young Adult (18-25)		Adolescent (13-18)		Child (8-12)		Young Child (5-7)		Toddler (2-4)
Self-report	Parent proxy-report	Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

*The Cognitive Functioning Scale is a part of the PedsQLTM Multidimensional Fatigue Scale

PedsQL™ Diabetes Module 3.0 version

Please specify: Standard ☐ Acute ☐ Both ☐

Young Adult (18-25)	Adolescent (13-18)	Child (8-12)	Young Child (5-7)	Toddler (2-4)

Self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Child self-report	Parent proxy-report	Parent proxy-report
☐	☐	☐	☐	☐	☐	☐	☐	☐

Financing of the Project:

x☐ Not funded academic research/project, individual medical practice	*Projects not explicitly funded, but funding comes from overall departmental funds or from the University or individual funds.*
☐ Funded academic research/project	*Projects receiving funding from commerce, government, EU or registered charity.* ***Funded academic research– sponsored by industry- fits the "commercial study/project" category.***
☐ Large non-commercial organization Research and Evaluation (per-study license)	*Large non-commercial organization Research and Evaluation; e.g. states, nations, hospitals, healthcare systems (includes an important number of patients and/or centres)*
☐ Large non-commercial organization Unlimited Research and Evaluation and clinical use (annual license, unlimited use)	*Large non-commercial organization Research and Evaluation; e.g. states, nations, hospitals, healthcare systems (includes an important number of patients and/or centres)* Please specify number of centres----------
☐ Large non-commercial organization Unlimited Research and Evaluation and clinical use (Patient Registry)	*Large non-commercial organization Research and Evaluation; e.g. states, nations, hospitals, healthcare systems* *Patient Registry: an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves a predetermined scientific, clinical, or policy purposes* Please specify number of patients----------
☐ Commercial study	*Commercial studies (industry, CRO, any for-profit companies)* Please specify number of centres----------
☐ Commercial Patient Registry	*Commercial studies (industry, CRO, any for-profit companies)* *Patient Registry: see above* Please specify number of patients----------
Grants / Sponsoring from (if any) *(name of the governmental/ foundation/company or other funding/sponsoring source):*	....

Section 2.02 Conditions for use

The User undertakes to use the Questionnaire in accordance with the conditions for use defined hereafter.

(a) Rights transferred

Acting in the Owner's name, MRT transfers the following limited, non-exclusive rights, to the User (the "Limited Rights")
(i) to use the Questionnaire, only as part of the Study; this right is made up exclusively of the right to communicate it to the Beneficiaries only, by any means of communication and by any means of remote distribution known or unknown to date, subject to respecting the conditions for use described hereafter; and

(ii) to reproduce the Questionnaire, only as part of the Study; this right is made up exclusively of the right to physically establish the Questionnaire or to have it physically established, on any paper, electronic, analog or digital medium, and in particular documents, articles, studies, observations, publications, websites whether or not protected by restricted access, CD, DVD, CD-ROM, hard disk, USB flash drive, for the Beneficiaries only and subject to respecting the conditions for use described hereafter; and

(iii) Should the Questionnaire not already have been translated into the language requested, the User is entitled to translate the Questionnaire or have it translated in this language, subject to informing MRT of the same beforehand by the signature of a Translation Agreement indicating the terms of it and to providing a copy of the translation thus obtained as soon as possible to MRT.

(iiii) In the context of commercial studies or any project funded by the pharmaceutical industry, the User undertakes to have the Questionnaire translated in this language by Mapi Language Services. Mapi Language Services is the only organization authorized by the Owner to perform linguistic validation/translation work on the Questionnaire.

The User acknowledges and accepts that it is not entitled to amend, modify, condense, adapt, reorganise the Questionnaire on any medium whatsoever, in any way whatsoever, even minor, without MRT's prior specific written consent.

(b) Specific conditions for the Owner

The Owner has intended to transfer a part of the copyright on the Questionnaire and/or the Documentation to MRT in order to enable MRT to make it available to the User for the purpose of the Study, subject to the User respecting the following conditions: User shall not modify, abridge, condense, translate, adapt, recast or transform the Questionnaire in any manner or form, including but not limited to any minor or significant change in wordings or organisation in the Questionnaire, without the prior written agreement of the Owner. If permission is granted, any improvements, modifications, or enhancements to the Questionnaire which may be conceived or developed, including translations and modules, shall become the property of the Owner. The User therefore undertakes to respect these special terms.

(c) Specific conditions for the Questionnaire

- Use in Individual clinical practice or Research study / project

The User undertakes never to duplicate, transfer or publish the Questionnaire without indicating the Copyright Notice.

In the case of use of an electronic version of the Questionnaire in academic studies, the User undertakes to respect the following special obligations:

- In case of use of an IT Company (e-vendor), User shall check with Mapi Research Trust that IT Company has signed the necessary License Agreement with Mapi Research Trust before developing the electronic version of the Questionnaire
- Not modify the questionnaire (items and response scales, including the response scale numbers from 0-4)
- Cite the reference publications
- Insert the Owner's copyright notice on all pages/screens on which the Questionnaire will be presented and insert the Trademark information: PedsQL™, Copyright © 1998 JW Varni, Ph.D. All rights reserved.
- Mention the following information: "PedsQL™ contact information and permission to use: Mapi Research Trust, Lyon, France – Internet: https://eprovide.mapi-trust.org and www.pedsql.org/index.html "
- Submit the screenshots of all the Pages where the Questionnaire appears to Dr James W. Varni before release for approval and to check that the above-mentioned requirements have been respected.

In the case of use of an electronic version of the Questionnaire in commercial studies / projects, the User undertakes to respect the following special obligations:
User shall:

- In case of use of an IT Company (e-vendor), User shall check with Mapi Research Trust that IT Company has signed the necessary License Agreement with Mapi Research Trust before developing the electronic version of the Questionnaire
- Not modify the questionnaire (items and response scales, including the response scale numbers from 0-4)
- Cite the reference publications
- Insert the Owner's copyright notice on all pages/screens on which the Questionnaire will be presented and insert the Trademark information: PedsQL™, Copyright © 1998 JW Varni, Ph.D. All rights reserved.
- Mention the following information: "PedsQL™ contact information and permission to use: Mapi Research Trust, Lyon, France– Internet: https://eprovide.mapi-trust.org and www.pedsql.org/index.html "

- For the first migration of the Questionnaire (generally the original version) into a specific electronic device
    - Review of screenshots:

After implementation of the Questionnaire into the device, the user/IT Company will generate screen captures (screenshots) of the original questionnaire as displayed in the device. These will be reviewed by Mapi to check that they are consistent with the original paper version in terms of presentation, content and completion except for specific instructions related to the electronic administration. Corrections that may be needed will be reported to the user/IT Company. In this case, screenshots after correction will be generated for another round of review by Mapi until all screenshots are approved.
Dr James W. Varni will review all approved screenshots for a final validation.

- Usability testing:

Usability testing is a methodology which aims to examine whether respondents are able to use a device and associated software as intended. Major issues of concern in usability testing typically include device complexity, navigation and response selection for example.
The objective of this investigation is to ensure that the electronic version of the questionnaire as included in the device meets usability criteria, focusing on functional aspects and respondents' understanding of instructions.
Usability testing consists in interviews with patients where patients will complete the electronic version of the Questionnaire on the device and comment on their understanding of the instructions, ease of use and handiness of the device. A Usability testing report presenting results will be produced. If any changes are recommended, these will be implemented by the user/IT Company. If issues raised by respondents are rated as major, the user/IT Company may need to perform additional developments and another round of interviews may be needed.
Dr James W. Varni will review the changes suggested, if any, following the interviews.

The review of screenshots is mandatory. The usability testing is highly recommended by Mapi, however should the User and/or IT Company decide not to perform this step, Mapi Research Trust shall not be held responsible for any consequence and expense associated with this decision which shall remain the User and/or IT Company's sole liability.

The review of screenshots and usability testing, when and if performed, shall be performed exclusively by Mapi and shall be sponsored by the User.

The performance of the review of screenshots and usability testing will result in a certification of the electronic device original version of the Questionnaires by Mapi for future licenses.

- For the migration of other language versions of the Questionnaire on an existing certified specific electronic device

  - Update version

After the electronic device original version of the Questionnaire is fully ready, the Questionnaire's language versions developed for paper administration will be updated to reflect the changes in wording of instructions implemented in the electronic device original version of the questionnaire.
Native speakers of the languages will reflect the changes made to the electronic device original version of the Questionnaire and will provide English equivalents of all changes made for Mapi's quality control.

  - Review of screenshots:

After implementation of the Questionnaire into the device, the user/IT Company will generate screen captures (screenshots) of the original questionnaire as displayed in the device. These will be reviewed by Mapi to check that they are consistent with the original paper version in terms of presentation, content and completion except for specific instructions related to the electronic administration. Corrections that may be needed will be reported to the user/IT Company. In this case, screenshots after correction will be generated for another round of review by Mapi until all screenshots are approved.

The update of version and review of screenshots are mandatory. These steps shall be performed exclusively by Mapi and shall be sponsored by the User.

The performance of the update of version and review of screenshots will result in a certification of the electronic device language version of the Questionnaires by Mapi for future licenses.

- Use in a publication:

In the case of a publication, article, study or observation on paper or electronic format of the Questionnaire, the User undertakes to respect the following special obligations:

- not to include any full copy of the Questionnaire, but a version with the indication "sample copy, do not use without permission"
- to indicate the name and copyright notice of the Owner (PedsQL™, Copyright © 1998 JW Varni, Ph.D. All rights reserved)
- to include the reference publications of the Questionnaire
- to indicate the details of MRT for any information on the Questionnaire as follows: PedsQL™contact information and permission to use: Mapi Research Trust, Lyon, France.Internet: https://eprovide.mapi-trust.org and www.pedsql.org
- to provide MRT, as soon as possible, with a copy of any publication regarding the Questionnaire, for information purposes
- to submit the screenshots of all the Pages where the Questionnaire appears to MRT before release to check that the above-mentioned requirements have been respected.

- Use for dissemination or marketing:

In the case of use in a dissemination/marketing context:

- On a website with unrestricted access:

The publication of a copy of the PedsQL™ on a website with unrestricted access is not permitted.

- On a website with restricted access:

In the case of publication on a website with restricted access, the User may include a version of the Questionnaire that may be amended, subject to this version being protected by a sufficiently secure access to only allow the Beneficiaries to access it.

Article 3. TERM

MRT transfers the Limited Rights to use the Questionnaire as from the date of delivery of the Questionnaire to the User and for the whole period of the Study.

Article 4. BENEFICIARIES

The Parties agree that the User may communicate the Questionnaire in accordance with the conditions defined above to the Beneficiaries involved in the Study only, in relation to the Study defined in section 2.01.

Article 5. TERRITORIES AND LANGUAGES

MRT transfers the Limited Rights to use the Questionnaire on the following territories and in the languages indicated in the table below:

Language:	***For use in the following country***	***Language:***	***For use in the following country***	***Language:***	***For use in the following country***
-English	*-USA*				
Spanish-	*USA*				

Article 6. PRICE AND PAYMENT TERMS

The User undertakes in relation to MRT to pay the price owed in return for the availability of the Questionnaire, according to the prices set out in Appendix 3, depending on the languages requested and the costs of using the Questionnaire, in accordance with the terms and conditions described in section 6.02 of the General Terms included in Appendix 1.

Agreed and acknowledged by:

User's Name: Marion E. McRae

User's Title: Nurse Practitioner-Guerin Family Congenital Heart Program

User's Signature:

Date: 5/17/2016

Appendix 1 to the Special Terms:
User Agreement General Terms

User has read and accepted the MRT's General Terms of the Agreement, which are available on MRT's website: https://eprovide.mapi-trust.org/user-agreement-general-terms

Appendix 2 to the Special Terms:
References

Generic Core Scales:

- Varni JW, et al. The PedsQL™: Measurement Model for the Pediatric Quality of Life Inventory. *Medical Care*, 1999; 37(2):126-139
- Varni, J.W., et al. The PedsQL™ 4.0: Reliability and validity of the Pediatric Quality of Life Inventory™ Version 4.0 Generic Core Scales in healthy and patient populations. *Medical Care*, 2001; 39(8): 800-812.
- Varni, J.W., et al. (2002). The PedsQL™ 4.0 Generic Core Scales: Sensitivity, responsiveness, and impact on clinical decision-making. *Journal of Behavioral Medicine*, 25, 175-193.
- Varni, J.W., et al. (2003). The PedsQL™ 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. *Ambulatory Pediatrics*, 3, 329-341.
- Chan, K.S., Mangione-Smith, R., Burwinkle, T.M., Rosen, M., & Varni, J.W. (2005). The PedsQL™: Reliability and validity of the Short-Form Generic Core Scales and Asthma Module. *Medical Care*, 43, 256-265.
- Varni, J.W., & Limbers, C.A. (2009). The PedsQL™ 4.0 Generic Core Scales Young Adult Version: Feasibility, reliability and validity in a university student population. *Journal of Health Psychology*, 14, 611-622.

Asthma Module:

- Varni, J.W., Burwinkle, T.M., Rapoff, M.A., Kamps, J.L., & Olson, N. The PedsQL™ in pediatric asthma: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Asthma Module. *Journal of Behavioral Medicine*, 2004; 27:297-318.
- Chan, K.S., Mangione-Smith, R., Burwinkle, T.M, Rosen, M., & Varni, J.W. (2005). The PedsQL™: Reliability and validity of the Short-Form Generic Core Scales and Asthma Module. Medical Care, 43, 256-265.

Brain Tumor Module:

- Palmer, S.N., Meeske, K.A., Katz, E.R., Burwinke, T.M., & Varni, J.W. (2007). The PedsQL™ Brain Tumor Module: Initial reliability and validity. *Pediatric Blood and Cancer*, 49, 287-293.

Cancer Module:

- Varni, J.W., Burwinkle, T.M., Katz, E.R., Meeske, K., & Dickinson, P. The PedsQL™ in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*, 2002; 94: 2090-2106.
- Robert RS, Paxton RJ, Palla SL, Yang G, Askins MA, Joy SE, Ater JL. Feasibility, reliability, and validity of the pediatric quality of life inventory™ generic core scales, cancer module, and multidimensional fatigue scale in long-term adult survivors of pediatric cancer. *Pediatric Blood & Cancer* 2012;59:703–707.

Cerebral Palsy Module:

- Varni JW, Burwinkle TM, Berrin SJ, Sherman SA, Artavia K, Malcarne VL, Chambers HG (2006). The PedsQL™ in Pediatric Cerebral Palsy: Reliability, Validity, and Sensitivity of the Generic Core Scales and Cerebral Palsy Module. *Developmental Medicine and Child Neurology*, 48: 442-449.

Cardiac Module:

- Uzark, K., Jones, K., Burwinkle, T.M., & Varni, J.W. The Pediatric Quality of Life Inventory™ in children with heart disease. *Progress in Pediatric Cardiology*, 2003; 18:141-148.
- Uzark, K., Jones, K., Slusher, J., Limbers, C.A., Burwinkle, T.M., & Varni, J.W. (2008). Quality of life in children with heart disease as perceived by children and parents. *Pediatrics*, 121, e1060-e1067.

Cognitive Functioning Scale:

- McCarthy, M.L., MacKenzie, E.J., Durbin, D.R., Aitken, M.E., Jaffe, K.M., Paidas, C.N. et al. (2005). The Pediatric Quality of Life Inventory: An evaluation of its reliability and validity for children with traumatic brain injury. *Archives of Physical Medicine and Rehabilitation*, 86, 1901-1909.
- Varni, J.W., Burwinkle, T.M., Katz, E.R., Meeske, K., & Dickinson, P. (2002). The PedsQL™ in pediatric cancer: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales, Multidimensional Fatigue Scale, and Cancer Module. *Cancer*, 94, 2090-2106.
- Varni, J.W., Limbers, C.A., Sorensen, L.G., Neighbors, K., Martz, K., Bucuvalas, J.C., & Alonso, E.M. (2011). PedsQL™ Cognitive Functioning Scale in pediatric liver transplant recipients: Feasibility, reliability and validity. *Quality of Life Research*, 20, 913–921.

Diabetes Module:

- Varni, J.W., Curtis, B.H., Abetz, L.N., Lasch, K.E., Piault, E.C., & Zeytoonjian, A.A. (2013). Content validity of the PedsQL™ 3.2 Diabetes Module in newly diagnosed patients with Type 1 Diabetes Mellitus ages 8-45. *Quality of Life Research*. 22, 2169–2181.
- Varni, J.W., Burwinkle, T.M., Jacobs, J.R., Gottschalk, M., Kaufman, F., & Jones, K.L. The PedsQL™ in Type 1 and Type 2 diabetes: Reliability and validity of the Pediatric Quality of Life Inventory™ Generic Core Scales and Type 1 Diabetes Module. *Diabetes Care*, 2003; 26: 631-637.
- Nansel, T.R., Weisberg-Benchell, J., Wysocki, T., Laffel, L. & Anderson, B. (2008). Quality of life in children with Type 1 diabetes: A comparison of general and disease-specific measures and support for a unitary diabetes quality of life construct. *Diabetic Medicine*, 25, 1316-1323.
- Naughton, M.J., Ruggiero, A.M., Lawrence, J.M., Imperatore, G., Klingensmith, G.J. Waitzfelder, B., McKeown, R.E., Standiford, D.A., Liese, A.D., & Loots, B. (2008). Health-related quality of life of children and adolescents with type 1 or type 2 diabetes mellitus: SEARCH for Diabetes In Youth Study. *Archives of Pediatrics and Adolescent Medicine*, 162, 649-657.

- Hilliard, M.E., Lawrence, J.M., Modi, A.C., Anderson, A., Crume, T., Dolan, L.M., Merchant, A.T., Yi-Frazier, J.P., & Hood, K.K. (2013). Identification of minimal clinically important difference scores of the Pediatric Quality of Life Inventory in children, adolescents, and young adults with Type 1 and Type 2 diabetes. *Diabetes Care*, 36, 1891–1897.

Duchenne Muscular Dystrophy Module:

- Uzark, K., King, E., Cripe, L., Spicer, R., Sage, J., Kinnett, K., Wong, B., Pratt, J., & Varni, J.W. (2012). Health-related quality of life in children and adolescents with Duchenne Muscular Dystrophy. *Pediatrics*, 130, e1559-e1566.
-

End Stage Renal Disease Module:

- Goldstein, S.L., Graham, N., Warady, B.A., Seikaly, M., McDonald, R., Burwinkle, T.M., Limbers, C.A., & Varni, J.W. (2008). Measuring health-related quality of life in children with ESRD: Performance of the Generic and ESRD-Specific Instrument of the Pediatric Quality of Life Inventory™ (PedsQL™). *American Journal of Kidney Diseases*, 51, 285-297.

Eosinophilic Esophagitis:

- Franciosi, J.P., Hommel, K.A., Bendo, C.B., King, E.C., Collins, M.H., Eby, M.D., Marsolo, K., Abonia, J.P., von Tiehl, K.F., Putnam, P.E., Greenler, A.J., Greenberg, A.B., Bryson, R.A., Davis, C.M., Olive, A.P., Gupta, S.K., Erwin, E.A., Klinnert, M.D., Spergel, J.M., Denham, J.M., Furuta, G.T., Rothenberg, M.E., & Varni, J.W. (2013). PedsQL™ Eosinophilic Esophagitis Module: Feasibility, reliability and validity. *Journal of Pediatric Gastroenterology & Nutrition*, 57, 57-66.
- Franciosi, J.P., Hommel, K.A., Greenberg, A.B., Debrosse, C.W., Greenler, A.J., Abonia, J.P., Rothenberg, M.E., & Varni, J.W. (2012). Development of the Pediatric Quality of Life Inventory™ Eosinophilic Esophagitis Module items: Qualitative methods. *BMC Gastroenterology*, 12:135, 1-8.
- Franciosi J.P., Hommel, K.A., Debrosse, C.W., Greenberg, A.B., Greenler, A.J., Abonia, J.P., Rothenberg, M.E., & Varni, J.W. (2012). Quality of life in paediatric eosinophilic oesophagitis: What is important to patients? *Child: Care, Health and Development*, 38, 477–483.

Family Impact Module:

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- Steele, M.M., Steele, R.G., & Varni, J.W. (2009). Reliability and validity of the PedsQL™ Oral Health Scale: Measuring the relationship between child oral health and health-related quality of life. *Children's Health Care, 38*, 228-224.

Pediatric Pain Coping Inventory™:

- Varni, J.W., Waldron, S.A., Gragg, R.A., Rapoff, M.A., Bernstein, B.H., Lindsley, C.B., & Newcomb, M.D (1996). Development of the Waldron/Varni Pediatric Pain Coping Inventory. *Pain*, 67, 141-150.

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- Varni, J.W., Thompson, K.L., & Hanson, V. (1987). The Varni/Thompson Pediatric Pain Questionnaire: I. Chronic musculoskeletal pain in juvenile rheumatoid arthritis. *Pain*, 28, 27-38.

Present Functioning Visual Analogue Scales:

- Sherman, S.A., Eisen, S., Burwinkle, T.M., & Varni, J.W. (2006). The PedsQL™ Present Functioning Visual Analogue Scales: Preliminary reliability and validity. *Health and Quality of Life Outcomes*, 4:75, 1-10.

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Stem Cell Transplant Module:

- Lawitschka, A., Güclü, E.D., Varni, J.W., Putz, M., Wolff, D., Pavletic, S., Greinix, H., Peters, C., & Felder-Puig, R. (2014). Health-related quality of life in pediatric patients after allogeneic SCT: Development of the PedsQL™ Stem Cell Transplant Module and results of a pilot study. *Bone Marrow Transplantation*, 49, 1093–1097.

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Transplant Module:

- Weissberg-Benchell, J., Zielinski, T.E., Rodgers, S., Greenley, R.N., Askenazi, D., Goldstein, S.L., Fredericks, E.M., McDiarmid, S., Williams, L., Limbers, C.A., Tuzinkiewicz, K., Lerret, S., Alonso, E.M., & Varni, J.W. (2010). Pediatric health-

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Appendix 3 to the Special Terms:
Cost structure for the use of the PedsQL™ instruments

Cost structure for the use of the PedsQL™ instruments

- Not Funded Academic Research
  Not funded academic research: if your project is not explicitly funded, but funding comes from overall departmental funds or from the University or individual funds
- Funded Academic Research:
  Funded academic research: projects receiving funding from government, EU or registered charity
  Note: funded academic research sponsored by industry fits "commercial study" category
- Large non commercial organization research and evaluation:
  (e.g. States, Nations, Hospitals, Healthcare Systems; includes a large number of patients and/or centres.)
  - License fee per study
  - Annual license fee
  - Annual fee for Patient Registry
- Commercial Use:
  (Pharmaceutical Industry, CRO, any for-profit companies)
  - License fee per study
  - Annual license fee
  - Annual fee for Patient Registry

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- **Free of charge**

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(Funded academic research: projects receiving funding from government, EU or registered charity)
Note: funded academic research sponsored by industry fits "commercial study" category

- **License per study: 990 USD (or 883.48 EUR) including delivery of 1 module + 330 USD (or 294.50 EUR) per additional module**

Large non commercial organization research and evaluation:
(e.g. States, Nations, Hospitals, Healthcare Systems; includes a large number of patients and/or centres.)

Fees may be per study or based on a yearly contract for unlimited evaluation

1. **License per study:**

   - **Owner's Royalty Fees: 1 322.50 USD (or 1 180.20 EUR)**
   - **Mapi Research Trust's Distribution fees: 1 080 USD (or 963.80 EUR) including delivery of 1 module + 360 USD (or 321.26 EUR) per additional module**

2. **Annual license fee (i.e., unlimited use for one year):**

   - **Author's Annual Royalty Fees (1)**

3 centers or less	4 to 10 centers	11 to 15 centers	16 centers or more
6 647 USD *	13 260 USD *	19 872 USD *	26 485 USD *

** this fee includes 10% MRT's administrative fees*

   - **Mapi Research Trust's Annual Distribution Fees**

1 080 USD (or 963.80 EUR) including delivery of 1 module	+ 360 USD (or 321.26 EUR) per additional module

3. **Annual fee for Patient Registry:**

   - **Author's Annual Royalty Fees (1)**

200 patients or less	201 to 400 patients	401 to 600 patients	601 patients or more
6 647 USD *	13 260 USD *	19 872 USD *	26 485 USD *

** this fee includes 10% MRT's administrative fees*

   - **Mapi Research Trust's Annual Distribution Fees**

1 080 USD (or 963.80 EUR) including delivery of 1 module	+ 360 USD (or 321.26 EUR) per additional module

Commercial use:
(Pharmaceutical Industry, CRO, any for-profit companies)

Fees may be requested per study or based on a yearly contract

1. **license fee per study:**

   - **Author's Royalty Fees (1)**

3 centers or less	4 to 10 centers	11 to 15 centers	16 to 20 centers	21 to 25 centers
6 647 USD *	13 260 USD *	19 872 USD *	26 485 USD *	33 097 USD *

26 to 30 centers	31 to 35 centers	36 to 40 centers	41 to 45 centers	46 to 50 centers	51 or more centers
39 710 USD *	46 322 USD *	52 935 USD *	59 547 USD *	66 160 USD*	72 772 USD*

** this fee includes 10% MRT's administrative fees*

- **Mapi Research Trust's Distribution Fees**

Cost per PedsQL™ module	Cost per translation
1600 USD (or 1427.84 EUR)**	+ 500 USD (or 446.20 EUR) per existing translation of each module (regardless of the number of age-groups requested)

**including delivery of the requested modules in their original US English version

2. Annual license fee:

- **Author's Annual Royalty Fees*** (1)**

2 or 3 trials per year	4 to 6 trials per year	7 to 9 trials per year	10 to 12 trials per year	13 to15 trials per year	16 trials or more per year
33 097 USD *	39 710 USD *	46 322 USD *	52 935 USD *	59 547 USD *	66 160 USD *

** this fee includes 10% MRT's administrative fees*

- **Mapi Research Trust's Annual Distribution Fees*** (1)**

2 or 3 trials per year	4 to 6 trials per year	7 to 9 trials per year	10 to 12 trials per year	13 to15 trials per year	16 trials or more per year
3 510 USD**	5 590 USD**	8 515 USD**	11 440 USD**	14 365 USD**	16 315 USD**

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***Annual license is possible for a minimum of 2 studies, and for a duration of at least 1 year

3. Annual license fee for Patient Registry:

- **Author's Annual Royalty Fees*** (1)**

100 patients or less	101 to 200 patients	201 to 300 patients	301 to 400 patients	401 to 500 patients
6 647 USD **	13 260 USD **	19 872 USD *	26 485 USD *	33 097 USD *

501 to 600 patients	601 to 700 patients	701 to 800 patients	801 to 900 patients	901 to 1000 patients	1001 patients or more
39 710 USD *	46 322 USD *	52 935 USD *	59 547 USD *	66 160 USD*	72 772 USD*

** this fee includes 10% MRT's administrative fees*

- **Mapi Research Trust's Annual Distribution Fees**

Cost per PedsQL™ module	Cost per translation
1 600 USD (or 1 427.84 EUR)**	+ 500 USD (or 446.20 EUR) per existing translation of each module (regardless of the number of age-groups requested)

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