Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart Disease – International Study (APPROACH-IS): Rationale, design, and methods

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Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart Disease – International Study (APPROACH-IS): Rationale, design, and methods

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ABSTRACT

Background: Data on patient-reported outcomes (PROs) in adults with congenital heart disease (CHD) are inconsistent and vary across the world. Better understanding of PROs and their differences across cultural and geographic barriers can best be accomplished via international studies using uniform research methods. The APPROACH-IS consortium (Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study) was created for this purpose and investigates PROs in adults with CHD worldwide. This paper outlines the project rationale, design, and methods.

Methods/Design: APPROACH-IS is a cross-sectional study. The goal is to recruit 3,500-4,000 adults with CHD from 15 countries in five major regions of the world (Asia, Australia, Europe, North and South America). Self-report questionnaires are administered to capture information on PRO domains: (i) perceived health status (12-item Short-form Health Survey & EuroQOL-5D); (ii) psychological functioning (Hospital Anxiety and Depression Scale); (iii) health behaviors (Health-Behavior Scale–Congenital Heart Disease); and (iv) quality of life (Linear Analog Scale & Satisfaction With Life Scale). Additionally, potential explanatory variables are assessed: (i) socio-demographic variables; (ii) medical history (chart review); (iii) sense of coherence (Orientation to Life Questionnaire); and (iv) illness perceptions (Brief Illness Perception Questionnaire). Descriptive analyses and multilevel models will examine differences in PROs and investigate potential explanatory variables.

Discussion: APPROACH-IS represents a global effort to increase research understanding and capacity in the field of CHD, and will have major implications for patient care. Results will generate valuable information for developing interventions to optimize patients' health and well-being.

Registration: ClinicalTrials.gov: NCT02150603.

Key words: Adult; Heart defects, congenital; International cooperation; Methods; Patient-reported outcomes

1. Background

Worldwide, congenital heart disease (CHD) is the most common birth defect with a global prevalence of 9.3 per 1,000 newborns [1]. Over the past few decades, the number of adults with CHD has risen considerably as almost 90% of children with CHD now survive into adulthood [2, 3]. Adults with CHD now form more than 60% of the total CHD population [4]. These adults are confronted with life-long cardiac and non-cardiac challenges and comorbidities [5]. Hence, a strong need has been identified by the CHD community to attend to aspects important to the patient beyond the medical arena, such as psychosocial functioning and quality of life (QOL) [6]. As a result, there has been much interest in research assessing patient-reported outcomes (PROs) in adults with CHD. PROs are defined by the US Food and Drug administration as "*any reports of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else*" [7]. In addition to understanding the entire patient experience, PROs are of clinical significance in cardiovascular patient populations [8]. For example, poor perceived health status predicts hospitalization and mortality in patients with chronic heart failure and coronary artery disease [9]. Consequently, investigation of PROs within cardiovascular research is increasingly advocated [10].

Studies on perceived health status, health behaviors, psychological outcomes, and QOL in the field of CHD have reported inconsistent results. While some studies have shown that adults with CHD perceived their health status similar to controls [11, 12], others have found that perceived health status was lower in patients with CHD than in controls [13]. Several studies reported that patients with CHD displayed more emotional problems than their healthy counterparts [14-19]. For example, Kovacs et al. reported that 50% of patients met the

diagnostic criteria for at least one mood or anxiety disorder at some point in their lives [20]. However, a recent meta-analysis concluded that results on emotional problems are equivocal in the CHD research literature [21]. Prior research has highlighted the high prevalence of unhealthy behaviors in individuals with CHD. For instance, over half of young adults with CHD reported substance use in a Canadian study [22]. Numerous studies have demonstrated compromised QOL in patients with CHD [23]. However, existing data are not consistent, and several studies have indicated that outcomes in patients with CHD were comparable to healthy individuals [23-29], or even better than healthy peers [23]. For instance, studies conducted in the Netherlands [30] and Belgium [11] generally reported superior outcomes to those performed in the US [13]. As such, researchers are unsure to what extent their findings are generalizable worldwide. Furthermore, the role of potential explanatory variables (e.g., sense of coherence or illness perception) contributing to such international variation is not well understood.

This inconsistent pattern of findings raises important unanswered questions as to (i) whether differences in previously reported PROs are the result of methodological issues or regional differences; and if genuine differences do exist, (ii) whether influencing factors can be identified. Indeed, although PROs have been reported in many countries, scores may vary due to the influence of culture-bound or national factors on patients' subjective well-being [31]. However, variations between populations and regions may also be attributable to differences in study design and methodological shortcomings, such as small sample sizes and the use of questionnaires with weak psychometric properties [23]. No previous international study has focused on PROs in adults with CHD. Further, few studies in patients with CHD have included a comprehensive set of PROs.

Key questions about patient-reported health and well-being on a global stage can best be answered by a large international study in which a broad set of PROs is measured in a

uniform manner, and potentially influencing factors are obtained in all countries. Indeed, global challenges require global collaboration. This prompted the establishment of the APPROACH-IS consortium. APPROACH-IS is the acronym for Assessment of Patterns of Patient-Reported Outcomes in Adults with Congenital Heart disease – International Study. The purpose of this paper is to describe the rationale, design, and methods of APPROACH-IS, thereby providing a thorough background for future reports emerging from this project.

2. Study aims

The primary aim is to assess potential differences in four categories of PROs (perceived health status, psychological functioning, health behaviors, and QOL) in adults with CHD who are living in different areas of the world. The secondary aim is to gain insight into how international differences can be understood. For example, the present project focuses on potential differences in illness perceptions or sense of coherence to explain international variation in QOL.

3. Design and methods

3.1 Project design

APPROACH-IS is a large international, cross-sectional study conducted in collaboration with the International Society for Adult Congenital Heart Disease (ISACHD).

3.2 Settings

For this multi-country project, participating centers were selected by the APPROACH-IS steering committee based on feasibility (e.g., personnel and financial resources), willingness to participate, geographical distribution, and patient volume to ensure sufficient variability and recruitment of an adequate number of patients representing the entire spectrum of cardiac lesions (i.e., simple, moderate, and complex lesions). Overall, 24 centers across 15

countries (Argentina, Australia, Belgium, Canada, France, India, Italy, Japan, Malta, Norway, Taiwan, the Netherlands, Sweden, Switzerland, and USA) agreed to participate (Fig. 1).

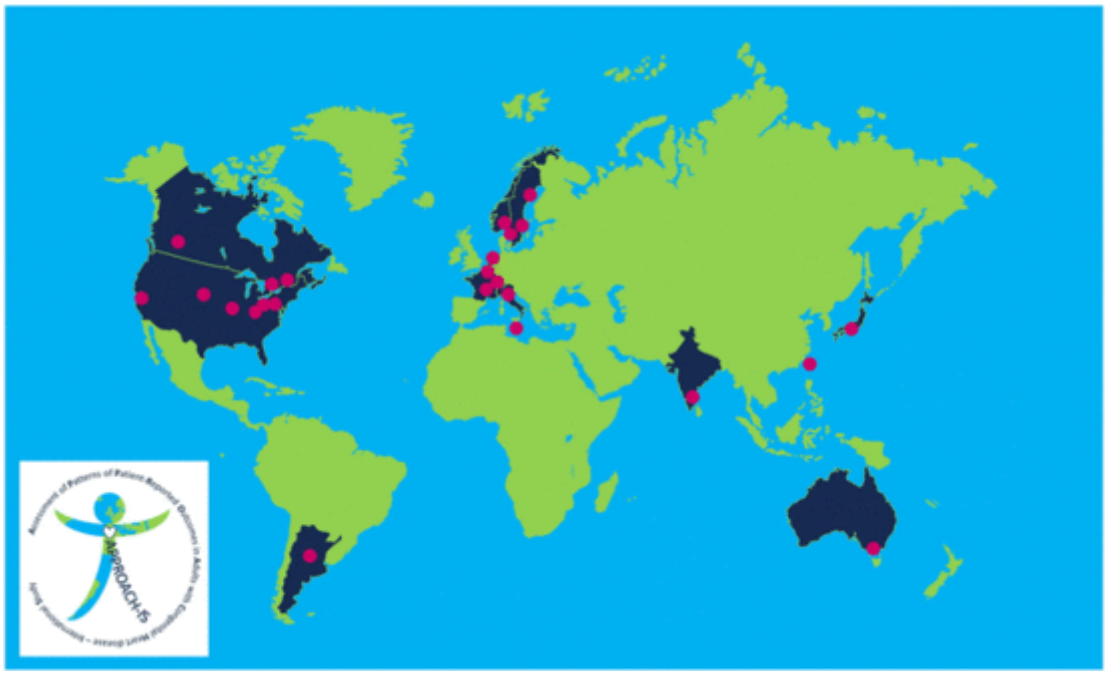

Fig. 1 Geographic distribution of the APPROACH-IS participating centers.

3.3 Sample

The recruitment goal of APPROACH-IS is to enroll 200 adults with CHD from each of the 24 participating centers, resulting in a sample size of 4,800 patients. However, in recognition of the fact that not all centers will be able to achieve this goal, we estimate that the total sample will be 3,500 to 4,000 patients. The inclusion criteria are as follows: (i) diagnosis of CHD, defined as a structural abnormality of the heart or intra-thoracic great vessels that is present at birth and is actually or potentially functionally significant (including mild, moderate, and severe heart defects) [32]; (ii) 18 years of age or older; (iii) diagnosis established before the age of 10 (i.e., before adolescence to warrant sufficient experience of living with CHD); (iv) continued follow-up at a CHD center or included in a national/regional registry; and (v) physical, cognitive, and language capabilities required to complete the self-report questionnaires. Patients are excluded from study participation if they (i) underwent

prior heart transplantation; (ii) have primary pulmonary hypertension; or (iii) have impaired cognitive abilities.

3.4 Project management

Coordination of APPROACH-IS is carried out by the University of Leuven (KU Leuven, Belgium). The coordinating center is responsible for the overall administration of the study, as managed by the international project coordinator (SA). Furthermore, the steering committee is responsible for overseeing all aspects of the international study, decision-making, and has final responsibility for scientific conduct. The steering committee is comprised of three investigators participating in this study, one nurse researcher (PM) and two psychologists (AK, KL). Each of the participating centers is overseen by the local principal investigator, who is responsible for all aspects of study implementation at the local level.

To streamline the processes of data collection and data management, standard operating procedures (SOPs) were developed for ethics approval; study preparation; study administration; recruitment and survey completion; data storage, entry and security; study progress; and publication policy. The SOPs allow for flexibility in terms of data collection (i.e., recruitment options) and data entry (i.e., online data entry vs. direct data entry into a statistical database). All data are transferred to the coordinating center where quality-control checks and statistical analyses are conducted. The coordinating center also created a website to share materials and methods (http://approach-is.net) **Error! Hyperlink reference not valid.**as well as distributing monthly information flashes to update the participating centers and other interested parties about study progress.

3.5 Data collection procedures

Participants are surveyed using a set of self-reported questionnaires. Participating centers can choose between two recruitment and data collection strategies. The first strategy is to randomly select eligible patients from their institution's database. These patients will then be mailed a study package including: (i) a study information letter; (ii) a copy of the survey package; (iii) the informed consent form (if required); and (iv) an addressed, prestamped return envelope. Patients are asked to complete the questionnaires within two weeks. Various approaches will be used to maximize response rates (e.g., mail or telephone reminders) [33]. However, to compensate for a potential nonresponse rate of up to 50%, which is generally anticipated in postal surveys [34], a minimum of 400 eligible patients per center will be selected. Three weeks after the first mail-out, a reminder will be sent to those who have not yet returned completed questionnaires. We expect a response rate of approximately 25% (i.e., 100 patients) after the initial mailing and hope to double the response through a reminder (i.e., 50% response rate or 200 patients) [35, 36].

A second recruitment strategy is to consecutively approach eligible patients at outpatient clinics. Patients who consent to participate will complete surveys during their clinic visit and return them to the research assistant or data collection officer. Patients may also be given the opportunity to return surveys by self-addressed stamped envelope.

In addition, regardless of the chosen recruitment strategy, a member of the research team from each participating center reviews participants' medical records in order to allow us to (i) describe the medical background of study participants and (ii) to investigate whether PROs vary as a function of medical variables. Data abstraction includes primary CHD diagnosis, disease complexity, surgical history, etc. Any documented history of a mood or anxiety disorder or other psychiatric diagnosis is also recorded.

Participating centers are individually responsible for the data collection process. Data collection for this project commenced in April 2013 and will be completed by December 2014.

4. Patient-reported outcome measures (PROs)

Participants complete a background information questionnaire focused on socio-demographic variables. The format of certain items varies between countries to reflect local standards (e.g., disability may be reported as a percentage or be divided into four categories).

Standardized questionnaires are used to measure primary and secondary outcomes. These questionnaires were chosen based on their sound psychometric properties, extensive use in previous studies, and availability in different languages. Table 1 presents an overview of the core battery of APPROACH-IS questionnaires and their psychometric properties.

If a certain questionnaire was not available in a specific language, a standard academic translation protocol was followed by the local research team. The protocol was comprised of the following steps: (i) forward translation; (ii) backward translation; (iii) pilot testing in patients; (iv) proofreading and finalization; and (v) report. All participating centers were advised to use the methodology as described by the Mapi Research Institute as a guide. Centers were asked to send the results of this process to the coordinating center. No substantial changes to the English template of the respective questionnaires were permitted.

Table 1
Variables measured in APPROACH-IS.

	Source	Measurements	Required translations	Validity	Reliability	Responsiveness	Interpretation
Socio-demographic variables							
- Age - Sex - Marital status - Presence of children - Student status - Educational level - Employment status - Patient-reported New York Heart Association assessment - Religion	Patient self-report	Survey developed by research team	Chinese, Dutch, French, German, Hindi, Italian, Japanese, Norwegian, Spanish, Swedish, and Tamil	NA	NA	NA	NA
Medical history							
- Congenital heart disease diagnosis - Complexity of heart defect - Cardiac surgeries/interventions - History of congestive heart failure/arrhythmia/other medical condition - Cardiac device implantation - Cognitive impairment - Frequency of follow-up - Cardiac admission (total number since age 18) - Chart-documented mood	Chart review	Survey developed by research team	Chinese, Dutch, French, German, Hindi, Italian, Japanese, Norwegian, Spanish, Swedish, and Tamil	NA	NA	NA	NA

or anxiety disorder or another psychiatric diagnosis							
Primary outcomes							
Perceived health status	Patient self-report	12-item Short-form Health Survey version 2 (SF-12)	NA	Confirmed in medical populations [40]	Confirmed in medical populations [40]	Confirmed in medical populations [40]	Scores from 0 to 100 on eight health domains; higher scores = better perceived health
		EuroQol-5D 3 level version (EQ-5D)	NA	Construct validity confirmed in cardiovascular patient populations [55]	Confirmed in cardiovascular patient populations [55]	Confirmed in cardiovascular patient populations [55]	Scores from 1 (no problems) to 3 (extreme problems) on five dimensions; score from 0 (worst imaginable health state) to 100 (best imaginable health state)
Psychological functioning	Patient self-report	Hospital Anxiety and Depression Scale (HADS)	NA	Confirmed in medical populations [56, 57]	Confirmed in medical populations [56, 57]	NR	Subscale scores range from 0 to 21; higher scores = more symptoms
Health behaviors	Patient	Health-Behavior	Chinese,	Content validity	Stability not	Confirmed in	Substance use

	self-report	Scale–Congenital Heart Disease (HBS-CHD)	French, German, Hindi, Italian, Japanese, Norwegian, Spanish, Swedish, and Tamil	and validity based on relationship with other variables confirmed in adolescents with congenital heart disease [44]	yet confirmed [44]	adolescents with congenital heart disease [44]	risk score (0-100); dental hygiene risk score (0-100); physical exercise score (0-∞); total health risk score (0-100)
Quality of life	Patient self-report	Linear Analog Scale (LAS)	Chinese, French, German, Hindi, Italian, Japanese, Norwegian, Spanish, Swedish, and Tamil	Test content and validity based on relationship with other variables confirmed in adults with congenital heart disease [11]	Test-retest reliability confirmed in adults with congenital heart disease [11]	Confirmed in adults with congenital heart disease [11]	Scores from 0 (worst imaginable quality of life) to 100 (best imaginable quality of life)
		Satisfaction with Life Scale (SWLS)	Tamil	Test content and validity based on relationship with other variables confirmed in adults with congenital heart disease [11]	Internal consistency and test-retest reliability confirmed in adults with congenital heart disease [11]	Confirmed in adults with congenital heart disease [11]	Total score from 5 (extremely dissatisfied) to 35 (extremely satisfied)
Secondary outcomes							
Sense of coherence	Patient	13 item Orientation	Tamil	Structural	Internal	Confirmed in	Total score

	self-report	to Life Questionnaire (SOC-13)		validity confirmed in adolescents with congenital heart disease [58]; Face, consensual, construct, criterion, and predictive validity confirmed in different populations [59]	consistency and test-retest reliability confirmed in different populations [59]	different populations [59]	from 13 to 91; higher values = stronger sense of coherence
Illness perceptions	Patient self-report	Brief Illness Perception Questionnaire (Brief IPQ)	Tamil	Concurrent validity confirmed in adults with renal disease, diabetes, and asthma; predictive validity confirmed in adults with myocardial infarction; discriminant validity confirmed in adults with	Test-retest reliability confirmed in adults with renal disease [53]	NR	Scores from 0 to 10 on eight dimensions; higher scores = more threatening view of the illness

						diabetes, asthma, colds, myocardial infarction, and chest pain [53]

NA: not applicable; NR: not reported.

4.1. Primary outcomes

Four PRO domains are measured: perceived health status, psychological functioning, health behaviors, and QOL (Table 1).

First, perceived health status is defined as the impact of a disease according to the patient, including symptoms, functional status, and health-related QOL [37]. We use two disease-generic measures to assess patients' perceived health status: the *12-item Short-Form Health Survey version 2* (SF-12v2) and the *EuroQol-5D 3 level version* (EQ-5D-3L). Studies have confirmed the psychometric properties of both scales, but for this project we chose to include both the SF-12 and EQ-5D to ensure coverage of a broad range of health dimensions [38, 39]. The SF-12 measures eight health domains: physical functioning, role participation with physical health problems, bodily pain, general health, vitality, social functioning, role participation with emotional health problems, and mental health. Scores range from 0 to 100 and higher scores reflect better perceived health status [40]. The SF-12 also produces a Mental Component Summary and a Physical Component Summary. The EQ-5D comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) which are rated at three levels (no problems, some problems, or extreme problems). The EQ-5D also includes a visual analog scale ranging from 0 (best imaginable health state) to 100 (worst imaginable health state) [41].

Second, we focus on two categories of psychological functioning, namely symptoms of anxiety and depression. The *Hospital Anxiety and Depression Scale* (HADS) was specifically developed for use with medical populations and produces two seven-item subscales (i.e., HADS-Anxiety and HADS-Depression). Subscale scores range from 0 to 21 with higher scores reflecting greater psychological distress [42]. Subscale scores of eight or higher reflect clinically-elevated symptomatology.

Third, health behaviors are defined as activities that a person undertakes to prevent disease or to improve health and well-being [43]. Two types of health behaviors can be distinguished: health enhancing (e.g., physical exercise) and health compromising behaviors (e.g., smoking). The *Health-Behavior Scale–Congenital Heart Disease* (HBS-CHD) was chosen to measure both behaviors. The HBS-CHD evaluates alcohol consumption (e.g., frequency), tobacco use (e.g., number of cigarettes), dental care (e.g., last dental visit), and physical activity (e.g., during leisure time). This information generates four risk scores: a substance use risk score (0-100), a dental hygiene risk score (0-100), a physical exercise score (0-∞), and a total health risk score (0-100). A higher risk score represents an unhealthier behavior [44].

Fourth, QOL was conceptually defined as the degree of overall life satisfaction [45]. A *Linear Analog Scale* (LAS) is the recommended method to rate overall QOL [45]. The LAS is a vertically oriented, 10-centimeter line graded with indicators from 0 (worst imaginable QOL) to 100 (best imaginable QOL) [45]. Furthermore, the *Satisfaction With Life Scale* (SWLS) is used as a second indicator of QOL and assesses a person's global judgment of life satisfaction [46]. The SWLS comprises five statements with a response scale ranging from 1 (strongly disagree) to 7 (strongly agree). A score of 20 represents the neutral point on the scale.

4.2. Secondary outcomes

Two psychosocial explanatory variables will also be measured (Table 1). The first is sense of coherence, representing a person's generalized world view that characterizes the extent to which a person perceives: (i) stimuli as structured and predictable; (ii) that resources are available to meet the demands posed by these stimuli; and (iii) that these demands are challenges worthy of investment. Hence, people with a strong SOC perceive the world as (i) comprehensible, (ii) manageable, and (iii) meaningful [47]. Previous studies in patients with

CHD have highlighted the importance of considering sense of coherence in relation to PROs [48, 49]. Therefore, sense of coherence is evaluated in this study using the 13-item *Orientation to Life Questionnaire* [47, 50]. A seven-point semantic differential scale ranging from 1 (very seldom or never) to 7 (very often) assesses the three components of sense of coherence: (i) comprehensibility (five items); (ii) manageability (four items); and (iii) meaningfulness (four items). The total score ranges from 13 to 91 with a higher score indicating a stronger sense of coherence.

Second, patients' illness perceptions will be evaluated. Illness perceptions are defined as the cognitive representations and beliefs that patients have about their illness [51] and have also been related to PROs in adults with CHD [52]. The *Brief Illness Perception Questionnaire* (Brief IPQ) is administered to assess cognitive and emotional representations of illness on a nine-item scale [53]. Items are rated from 0 to 10 and evaluate consequences, timeline, personal control, treatment control, identity (i.e., cognitive representations), concern, and emotions (i.e., emotional representations). The Brief IPQ also includes an item that assesses illness comprehensibility and another that inquires about perceived causal factors.

5. Quality control

Quality checks are performed by the coordinating center on data from the first 10 participants from each participating center. As such, any systematic errors can be addressed prior to further data entry. After performing preliminary analyses of all center-specific datasets to identify out-of-range and missing values, or possible remaining data entry errors, a cleaned version of these datasets will be organized into one overarching multi-country database.

6. Data analysis

First, descriptive and comparative analyses of PRO variables reflecting commonalities and differences will be performed. Data will be summarized separately for each participating center as counts and percentages for categorical variables and means and standard deviations for normally distributed continuous variables. Descriptive statistics will be reported for all participating centers and countries.

Second, relationships between PROs and potential explanatory variables will be examined. Special attention will be given to missing data by means of multiple imputation models. Sample size variations will be accounted for in the statistical methods. Given that the collected data is hierarchical, multilevel analysis will be employed. More specifically, data will be organized at three levels: (i) the individual patient level; (ii) the center level; and (iii) the country level. Individual patient data are nested within center and country levels (aggregate units). This project will allow for inter-country comparative analysis of the extent to which PROs differ, and in certain cases also for intra-country analysis (e.g., between American centers). Statistical significance will be defined as $p \leq 0.05$ with appropriate adjustments for multi-testing.

Given the richness of the data, substudies will be planned in accordance with ideas generated by participating centers. Substudies will be performed after the primary analyses have been conducted and reported.

7. Ethical issues

The overarching study protocol was approved by the Institutional Review Board of the University Hospitals Leuven/KU Leuven (i.e., the coordinating center). Additionally, ethical approval was obtained by each participating center, if required. Although informed consent will be obtained from all participants in most centers, there are some countries in which national legislation stipulates that written consent for survey studies is not required.

Maintaining participant confidentiality is deemed a high priority. No personal health information (e.g., name, medical record number, or date of birth) is sent from the participating centers to the coordinating center. A unique patient study identification code consists of a two-digit center identification code followed by a three-digit patient identification number. For example, code 01-001 represents the first patient recruited from the first participating center.

APPROACH-IS follows the recommendations of the Declaration of Helsinki II [54]. The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology. The study protocol was recorded at ClinicalTrials.gov: NCT02150603.

8. Current status of the project

We anticipate that data collection will be completed by the end of December 2014. Data quality checks and clarifications are performed on an ongoing basis. Data will be analyzed during the first six months of 2015. We foresee that the primary results of this study will be available in the second half of 2015.

9. Discussion

Adults with CHD represent a growing and aging patient population [2]. As survival rates continue to improve, patient well-being will continue to be a priority for healthcare professionals worldwide. At the present time, consistent data on PROs in adults with CHD from well-designed studies are lacking. The APPROACH-IS collaborative will provide a definitive contribution towards resolving this issue. As the largest collaborative thus far established across a wide cultural and regional diverse population, APPROACH-IS will extend the results from previous single-center or regional multi-center studies by incorporating collaborators from different regions in the world. The use of a strong, uniform

methodology will ensure consistent and reliable data, and will also lead to the further development of research capacity among all participating adult CHD centers. Furthermore, the resulting international dataset will be a valuable resource for researchers and healthcare professionals alike in the field of CHD. In addition, data may serve as a historical cohort to which future samples may compare. Indeed, APPROACH-IS will generate a comparable dataset from adult CHD centers around the world whose pooled results can inform (inter)national policy.

A few study limitations must be acknowledged. First, APPROACH-IS is a cross-sectional study, and thus causality cannot be determined. However, some centers have opted to follow the participants on a longitudinal basis. Second, study results may not be generalizable to patients with CHD who are not being followed in CHD programs in participating countries, to adults with CHD in other countries, or to patients who do not receive ongoing CHD follow up. Third, patients who are physically or mentally not capable of completing the questionnaires are not represented in this study. Fourth, we acknowledge that it is not possible to determine the impact of all possible factors (e.g., undiagnosed syndromes or family history of mental health problems) on PROs.

In summary, APPROACH-IS should result in significant scientific and clinical contributions by increasing our understanding of PROs in adults with CHD, with the focus on international differences and potential explanatory variables. As such, we hope that this project will prompt the development of future interventions designed to address the health and well-being of patients with CHD around the world.

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