A Life Less Ordinary
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Chapter 4
Adapted from:

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 through 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
APPROACH-IS is a cross-sectional study. The goal is to recruit 3500–4000 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 behaviours (Health-Behaviour 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.

Conclusion
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.
INTRODUCTION

Worldwide, congenital heart disease (CHD) is the most common birth defect with a global prevalence of 9.3 per 1000 new-borns. 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. Adults with CHD now form more than 60% of the total CHD population. These adults are confronted with life-long cardiac and non-cardiac challenges and comorbidities. Hence, a strong need has been identified by the CHD community to attend to aspects important to the patient beyond the medical field, such as psychosocial functioning and quality of life (QOL). 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”. In addition to understanding the entire patient experience, PROs are of clinical significance in cardiovascular patient populations. For example, poor perceived health status predicts hospitalization and mortality in patients with chronic heart failure and coronary artery disease. Consequently, investigation of PROs within cardiovascular research is increasingly advocated.

Studies on perceived health status, health behaviours, 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, others have found that perceived health status was lower in patients with CHD than in controls. Several studies reported that patients with CHD displayed more emotional problems than their healthy counterparts. 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. However, a recent meta-analysis concluded that results on emotional problems are equivocal in the CHD research literature. Prior research has highlighted the high prevalence of unhealthy behaviours in individuals with CHD. For instance, over half of young adults with CHD reported substance use in a Canadian study. Numerous studies have demonstrated compromised QOL in patients with CHD. However, existing data are not consistent, and several studies have indicated that outcomes in patients with CHD were comparable to healthy individuals, or even better than healthy peers. For instance, studies conducted in the Netherlands and Belgium generally reported superior outcomes to those performed in the US. 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 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. 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. 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.

**Study aims**

The primary aim is to assess potential differences in four categories of PROs (perceived health status, psychological functioning, health behaviours, 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.

**METHODS**

**Project design**

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

**Settings**

For this multi-country project, participating centres 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 severe or complex lesions).
Overall, 24 centres across 15 countries (Argentina, Australia, Belgium, Canada, France, India, Italy, Japan, Malta, Norway, Taiwan, the Netherlands, Sweden, Switzerland, and USA) agreed to participate (Figure 1).

The recruitment goal of APPROACH-IS is to enrol 200 adults with CHD from each of the 24 participating centres, resulting in a sample size of 4800 patients. However, in recognition of the fact that not all centres will be able to achieve this goal, we estimate that the total sample will be 3500 to 4000 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)\(^2\); (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 centre 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.

Coordination of APPROACH-IS is carried out by the University of Leuven (KU Leuven, Belgium). The coordinating centre 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 centres 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 centre where quality-control checks and statistical analyses are conducted. The coordinating centre also created a website to share materials and methods (http://approach-is.net) as well as distributing monthly information flashes to update the participating centres and other interested parties about study progress.

Data collection procedures

Participants are surveyed using a set of self-reported questionnaires. Participating centres 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 centre 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 centre 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 centres are individually responsible for the data collection process. Data collection for this project commenced in April 2013 and will expected to be completed by December 2014.

**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 centres were advised to use the methodology as described by the Mapi Research Institute as a guide. Centres were asked to send the results of this process to the coordinating centre. No substantial changes to the English template of the respective questionnaires were permitted.

**Primary outcomes**

Four PRO domains are measured: perceived health status, psychological functioning, health behaviours, 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 analogue 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 behaviours are defined as activities that a person undertakes to prevent disease or to improve health and well-being \(^{43}\). Two types of health behaviours’ can be distinguished: health enhancing (e.g., physical exercise) and health compromising behaviours (e.g., smoking). The Health-Behaviour Scale-Congenital Heart Disease (HBS-CHD) was chosen to measure both behaviours. 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–\(\infty\)), and a total health risk score (0–100). A higher risk score represents an unhealthier behaviour \(^{44}\).

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. 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.

**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\textsuperscript{51} and have also been related to PROs in adults with CHD\textsuperscript{52}. The Brief Illness Perception Questionnaire (Brief IPQ) is administered to assess cognitive and emotional representations of illness on a nine-item scale\textsuperscript{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 enquires about perceived causal factors.

Quality control
Quality checks are performed by the coordinating centre on data from the first 10 participants from each participating centre. As such, any systematic errors can be addressed prior to further data entry. After performing preliminary analyses of all centre-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.

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 centre 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 centres 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 centre level; and (iii) the country level. Individual patient data are nested within centre 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 centres). Statistical significance will be defined as $p \leq 0.05$ with appropriate adjustments for multi-testing. Given the richness of the data, sub studies will be planned in accordance with ideas generated by participating centres. Sub studies will be performed after the primary analyses have been conducted and reported.
**Ethical issues**

The overarching study protocol was approved by the Institutional Review Board of the University Hospitals Leuven/KU Leuven (i.e., the coordinating centre). Additionally, ethical approval was obtained by each participating centre, if required. Although informed consent will be obtained from all participants in most centres, 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 centres to the coordinating centre. A unique patient study identification code consists of a two-digit centre identification code followed by a three-digit patient identification number. For example, code 01–001 represents the first patient recruited from the first participating centre. APPROACH-IS follows the recommendations of the Declaration of Helsinki II. The study protocol was recorded at ClinicalTrials.gov: NCT02150603.

**DISCUSSION**

Adults with CHD represent a growing and aging patient population. 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-centre or regional multi-centre 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 centres. 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 centres 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 centres 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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