PROTOCOL:
Improving Cardiac Rehabilitation (CR) Care through the International Cardiac Rehabilitation Registry (ICRR)
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Introduction

Cardiovascular diseases (CVDs) are among the leading burdens of morbidity and disability, with particularly high impact in lower-resource settings.[1] Cardiac rehabilitation is a guideline-recommended model of secondary preventive care for the optimal management of CVD.[2-7] It has been shown to reduce cardiovascular morbidity (including expensive hospitalizations and revascularization procedures) and mortality by 20%, while significantly improving patient's quality of life.[8] Further, CR is highly cost-effective.[9]

However, the degree of patient benefit is affected by the extent of CR utilization as well as the quality of CR services. A CR registry could track enrollment in patients referred to the program, adherence and completion in those enrolling, as well as the quality of care patients receive and their outcomes; thus, it could pinpoint areas where improvement strategies are needed.

Clinical registries are key means for health care standardization and quality assurance.[10-12] Registries should be used for conditions that are highly prevalent, where there are serious consequences associated with poor quality care, and the condition costs a lot to the healthcare system;[11] CVD certainly fits all these criteria. Registries involve systematic collection of clinical data which are used for assessment of the appropriateness (process) and effectiveness (outcomes) of health care.[14] Therefore, registries provide a strong evidence base on effectiveness and quality of healthcare provided to patients.[11]

Clinical guidelines/statements recommend evaluation as a "standard" for CR programs [10. 13, 14] to monitor health care and outcomes of patients through systematic data collection and provision of timely feedback. Registries can inform policies for CR improvement or guideline updates, as well as support research testing the effectiveness and cost-effectiveness of CR in areas where it is not yet investigated.[15]

Despite the recommendations and potential benefits, there are few CR registries around the globe. A systematic review[16] and recent investigation by the International Council of Cardiovascular Prevention and Rehabilitation (ICCPR), suggests there are only currently CR registries in Australia, Austria, Japan, United States, Denmark, United Kingdom, and Sweden, and China. As you can see, most of these are in higher-resource settings. Clearly, there is great need for a CR registry that could be feasibly used internationally, and particularly in low-resource settings where CR need is greatest, evidence is least available, and programs are being developed currently.

Objective(s)

The aim of this project is to develop the International CR Registry (ICRR), a health services registry to establish the quality of CR delivery, and the effectiveness in terms of patient outcomes, in low-resource settings. The purposes of the registry are care optimization, evidentiary support for CR advocacy / policy, and research. Given CR is burgeoning in low-

resource settings, the ICRR may support standardization and optimization of CR delivery internationally. By demonstrating efficacy, CR programs and associations can advocate for coverage.

Methods

This is a prospective registry. The design is longitudinal and observational.

In summary, to launch and sustain a global CR registry (ICRR), will involve first inviting sites to participate and on-boarding them. Then, the data steward from the participating CR programs will enter data on patients who do not opt-out anonymously. Patients may also report data directly. We will benchmark quality of care and patient outcomes with other countries and over time anonymously, through registry dashboards.

Procedure

After the registry is piloted through our previously-approved usability testing phase, all programs in low-resource settings will be welcome to participate at no cost; sites will be invited through ICCPR's global CR program email distribution list (it is voluntary for programs to opt-in), ICCPR member associations and friends as well as ICCPR's social media channels (twitter, youtube, facebook).

Interested programs will be asked to complete the program survey (appended; to be administered via REDCap), sign an ICRR agreement/ get institutional approvals, secure ethics approval from their local board, and undergo training by the user sub-committee before joining the ICRR officially.

Sites will provide patients with the registry information letter, which has details on opting-out as per their approved protocol (e.g., emailed before first visit, provided in person at first visit). All participating sites will provide program-reported variables for patients who do not opt out. Some sites may be able to arrange electronic data capture for the program-reported variables to contribute data to the registry, rather than manual electronic entry. Arrangements with institutional privacy and IT departments would need to be approved at the local level, to ensure security is maintained as per this protocol.

Programs will follow procedures approved by their local ethics board for collection of patient-reported variables (e.g., sites opting in to patient report will secure contact information from willing patients; this may require a consent form depending on the locally-approved protocol). The patient's mobile number and/or email (based on their preference) will be entered into the registry where the patient agrees, to trigger the patient surveys at each time point. If a patient is not able to complete the survey for reasons of language or technology for example and would like to denote a substitute for themselves, that contact information will be entered.

Dendrite sends 1 reminder to non-responding patients 1 week from initial correspondence. Patients can opt-out of follow-up surveys at any time by emailing ICRR; this is stated in every email sent to patients with contact information.

Where direct provision of data by patients is not approved at a CR site, or the institutional review board approves patient report but patients do not have a mobile device/computer/tablet/ or technical savvy to complete online surveys, programs may collect this data directly from patients and enter it to the registry, if approved by their local ethics board. This may involve a paper report form, again if approved by the local ethics board, which would be immediately destroyed upon entry into the registry. Otherwise, there are no paper case report forms.

If the site has translated the registry information letter and/or consent form and this was approved by the local ethics board, they may ask the questions of patients verbally in this non-English language or ask them to provide answers on paper (questions translated) in this same language.

Data provision by sites is voluntary. Sites will be encouraged to enter data on all patients meeting inclusion / exclusion criteria to reduce bias. Prospective / concurrent data collection will be encouraged, to support quality improvement activities. The dashboards show change over time in 6-month increments; Sites will be encouraged to continue to provide data on new patients until all indicators show quality as possible. Sites will be supported in quality improvement by the ICRR user sub-committee as desired.

Once all interested sites are on-boarded and quality improvement supports have been implemented with interested sites by the user sub-committee, we will invite a random sample of programs from low-resource World Health Organization regions that are under-represented in the registry to reduce bias.

Population: Sites / Patients

SITES: CR programs in low-resource settings (i.e., low or middle-income country according to World Bank, or in region within a higher-income country where there is under-development of CR related to financial resources, lack of healthcare system resources, lack of patient and provider awareness, and/or patient disadvantage [e.g., limited social resources, geographic barriers]) are eligible to join the registry. A CR program is defined as one that offers initial assessment, structured exercise (can be supervised or unsupervised) and at least one other strategy to control risk factors. The registry pertains to phase II CR. Programs that cannot enter data in English will be excluded.

Through our global audit and survey of CR programs, we estimate there are approximately ~3000 CR programs (excluding Australia, US and UK which have established registries, among a

few other countries), and each serves a median of 250 patients / year[17] (note we do not expect this many programs to take part).

PATIENTS: Coronary heart disease patients who are indicated for CR[18] are eligible for registry inclusion (e.g., acute coronary syndrome +/- revascularization, heart failure, stable coronary artery disease +/- valve or rhythm conditions); there are some exclusions to eligibility such as inability to ambulate.[19] Patients who are not capable to understand the registry information letter for cognitive or mental reasons will be excluded (although they would also likely be excluded from CR). Patients who are not proficient in the language of the local ethics-approved registry information letter and opt-out form (i.e., sites may translate the letter) will also be excluded.

Patient sample size will be dependent upon the number of participating CR programs, as well as their patient volumes and the proportion of their patients who do not opt-out upon provision of the registry information letter (appended).

Measures

In addition to the program survey, there is a registry variable list for patient-level data. The development process was adapted from recommendations of the Core Outcome Set-STAndards for Development (COS-STAD).[20] The following sources were considered in the development of the initial variable list: AHRQ's Outcome Measures Framework (characteristics, treatment, outcomes),[21] relevant outcome measure sets from the COMET initiative (https://www.comet-initiative.org/),[22] the International Consortium for Health Outcomes Measurement Coronary Artery Disease standard set,[23] literature on patient preferences for outcome measures,[24] the variable lists of all available CR registries except Australia and Japan,[16] all globally-available sets of quality indicators,[25] and WHO's Package of Rehabilitation Interventions for ischemic heart disease (based on best CR guidelines). The final variable list and data dictionary were then developed through a delphi process approved by York University's Office of Research Ethics (Toronto, Canada).

There are 10 program-reported variables and 16 patient-reported variables (note some variables are assessed at multiple time points- this is denoted in the data dictionary), assessed pre-program, post-program (dependent upon duration of each program) and each year from initial assessment (until patients expire or are unable to complete the assessments, which would be ascertained by the program, or opt-out).
The registry has pre-specified out-of-range values for all continuous variables. The definitions are available in the registry when a user hovers over the variable.
The registry has a data quality dashboard which displays by site completeness of data entry at each time point, to help reduce bias. The registry has in-built minimum and maximum values for continuous variables to reduce data entry errors. The data dictionary clearly defines each variable, and new sites are trained prior to start. The registry is being usability tested prior to launch. The research sub-committee will oversee a data quality process.

Statistical Analyses

Descriptive statistics, i.e. means and standard deviations for continuous variables and frequencies with percentages for categorical variables, will be used to describe the quality of care (outcomes above), and quality of the data (e.g. percentage of records with complete data, or the proportion of variables that were captured by the registry). For testing some of the patient outcomes (pre-post program), paired t-tests will also be used for continuous variables and chi-square test for categorical variables.

Univariate and multivariable approaches will be used to identify factors associated with measures of interest, including the use of guideline-indicated therapies. Associations between patient characteristics and outcomes of interest via logistic regression will be reported with odds ratios and 95% confidence intervals. Associations will be considered statistically significant when 2-sided α is <0.05. To limit the influence of confounding, multivariable adjustment will be used, including propensity weighting, or other techniques. Appropriate statistical corrections for repeated measures will be performed.

Note data audits may be supported by a registry database analyst / professional statistician. Risk adjustment (e.g., socioeconomic status, indication, comorbidities, age) or propensity score matching will be considered.

Timelines

The work plan will be as follows:

1- Ethics approval - York U; (Fall 2020).

2- Set up ICRR site governance (Fall/20 and winter 2021)- user sub-committee will finalize site agreements, process to on-board sites, support each to get ethics approval, train them, and start entering data on willing patients anonymously (note sites can onboard at any time once this process is set up)

3- Auditing and benchmarking with best practices across sites/ countries (Spring 2021-ongoing).

Ethical Considerations

All new patients to the ICRR-participating CR programs will be provided an informational letter about the registry, and the opportunity to opt out. Patient consent for program report of data will not be solicited. As demonstrated by Tu et al. (2004)[26], requiring informed consent for registries leads to selection biases which render the sample unrepresentative of the typical patient. We therefore propose to waive the requirement of informed consent for this minimal risk observational research.

Some institutional ethics boards may require patient consent to provide their contact information to provide data directly to the registry. For those sites, written informed consent will be sought from patients (drafted ICF attached; each institution's ethics board may request

some edits). Each site will store those securely in accordance with their institutional requirements, but at a minimum on a secure institutional server or in a locked cabinet in a locked office.

Patients contacting ICRR or their local CR site requesting not to further participate in the registry will have no further data contributed, and if the patient was providing data directly, we will ensure they will not receive any further correspondence. Those requesting withdrawal from the registry will have their data deleted; again if the patient was providing data directly, we will ensure they will not receive any further correspondence. Patients can also request their data. In addition to contacting their local program, they can do so through the ICRR patient website. A data processing agreement is in place between ICRR and Dendrite with protocols to achieve these.

POTENTIAL FUTURE USES OF ICRR DATA: Sites may also apply for ethics approval to survey patients over and above registry assessments. Sites may also apply for ethics approval for administrative data linkage (e.g., clinical databases, imaging or lab data, government databases or surveys), which could enable cost-effectiveness analysis for example. This would require some manner to identify patients probabilistically, and will require detailed consideration to mitigate the risk of re-identification. Moreover, in future interventions may be embedded (eg., stepped wedge designs with quality improvement initiatives). Other CR registries may collaborate to share aggregate data on common variables for policy and/or research purposes. All other research will undergo scrutiny by the research sub-committee and ethical review.

Data Handling & Security

Data will be extracted from medical records at each program and entered directly into the registry database; Each patient will have a unique registry ID and data shared with the registry is anonymous. Patients who agree will provide patient-reported outcomes directly.

Each site data steward shall maintain a password-protected excel file with only patient name and registry ID number. This is to facilitate collection of follow-up data. The file shall be stored only on a secure institutional server.

Dendrite will host the ICRR and ensure data security, to meet international data protection legislation for the duration of the contract. Dendrite has implemented over 170 major national/international registries and is an approved registry supplier. Dendrite's information security arrangements are regularly (every 12 months) assessed and certified by the UK Department of Health to ensure Dendrite's compliance with the strict information governance/security (Data Security and Protection Toolkit) requirements. Dendrite has successfully passed all assessments. The latest Dendrite's certification shows 'Standards Exceeded' – this is formally published on the Data Security and Protection Toolkit website: https://www.dsptoolkit.nhs.uk/OrganisationSearch?searchValue=8HJ38 Dendrite code is: 8HJ38. Dendrite's systems and processes are also regularly certified by CyberEssentials.

Dendrite will host the Registry on its' secure server in a protected data centre specifically designed for hosting confidential data (and they have a separate Canadian server which conforms with Canadian regulations). Data entered from sites into the registry is secured through encryption added to secure HTTP (i.e., https), done using Transport Layer Security. Stored data is also encrypted using InterSystems Cache database software.

Every CR site that contributes data to the registry will get access from Dendrite. Dendrite controls that each person has a unique login and password. Each site remains the owner of their site's data.

The two lead PIs of the registry (ICRR Executive) will take the ultimate responsibility for all data and its' access, under the oversight of ICCPR and ICRR committees. Any downloaded data files for analysis (e.g., annual reports, studies approved by ethics board) will be stored securely on York's server. These will only be stored for 10 years, at which point data will be destroyed. Registry data will be retained indefinitely. At a point where we may end the contract with Dendrite, the following steps for them to destroy the data will be taken:

- They will first export all the data from the registry, password protect it and place it on a secure server for ICRR to download.
- ICRR will download it to York University's secure server.
- Dendrite then destroys all the data the registry contains using "shredding" software (which uses the Guttman method) and then dismounts the registry.
- 2 weeks later (after a full 2-week back-up cycle has passed), Dendrite then produces a data destruction certificate, declaring that they no longer hold any of the registry Data. The data destruction certificate is forwarded to the Dendrite Data Protection Officer who puts it on the agenda for discussion / approval at the next (usually monthly) internal information governance meeting. Once approved, the data destruction certificate will be forwarded to ICRR.

The ICCR will explore potential public posting of anonymous registry data in a repository in future, to augment utility of the data through availability to the scientific community.

Funding & Governance

This study is a collaboration between Qatar University and York University, and will be funded by both institutes (York funding is in-kind). An agreement between QU and YU is executed. Funds are being used for a contract with Dendrite to host the registry.
Under the auspices of ICCPR, an ICRR steering committee has been formed which will oversee the ICRR implementation. The governance structure, including the user and research sub-committees, is shown here: https://globalcardiacrehab.com/International-CR-Registry-(ICRR).

Dissemination and Use of the Data

While sites will be able to view their own performance on the registry dashboards in real-time, any site benchmarking will show comparison data without identifying sites (i.e., no CR site will

know the performance of any other site, only aggregate data will be shown – one site versus others in region or world; or own site first 6 months vs latest 6 months). High-performing programs will be recognized on ICRR's website and ICCPR's social media accounts.
The following variables will be tracked in the dashboards, and hence available to participating CR sites:

- % of patients completing program (or only dropped out for clinical reason or R2W)
- Change in body mass index from pre to post-program
- Change in systolic blood pressure from pre to post-program
- Change in peak METs from pre to post-program
- Change in % pts using tobacco from pre to post
- Mean # supervised sessions attended
- Change in mins moderate to vigorous-intensity physical activity / week from pre to post-program
- Change in quality of life from pre to post-program
- Change in # servings fruit and veg from pre to post-program
- % of patients knowing what to do if have chest pain post-program
- % know their cholesterol and how to control post-program
- Mean medication adherence post-program, in patients that have funds for medications

Patients reporting data directly to the registry pre and post-program may receive a lay summary of their progress by the program which is generated in ICRR (to be posted on registry participant webpage https://globalcardiacrehab.com/ICRR-for-Patients).

Annual ICRR reports will be presented at webmeetings of key stakeholders (e.g., participating sites, policy-makers, ICCPR, CR associations) and shared on ICCPR's website and social media channels. All data reported will be anonymous and in aggregate. Lay summaries of these reports may be shared through newsletters to interested patient participants.

In future, ICCPR plans to develop a program accreditation process. CR programs will apply for accreditation consideration and be charged a fee (estimated to be $500USD). The anonymous data from the ICRR will be used to corroborate site quality, as well as responses to the ICRR program survey. Virtual site surveyance will also be undertaken. Renewal will be required every 2-3 years.

Any secondary use of the data for research purposes will go through separate ethical review. Requests will be vetted by the ICRR research sub-committee. No data will be released that could identify patients. This research may be published in peer-reviewed journals and presented at scholarly conferences.

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