

**PROMOTING PATIENT UTILIZATION OF CARDIAC REHABILITATION:**

**A JOINT INTERNATIONAL COUNCIL AND CANADIAN ASSOCIATION OF  
CARDIOVASCULAR PREVENTION AND REHABILITATION POSITION  
STATEMENT**

**Endorsed by:** Nepal Physiotherapy Society (NEPTA)

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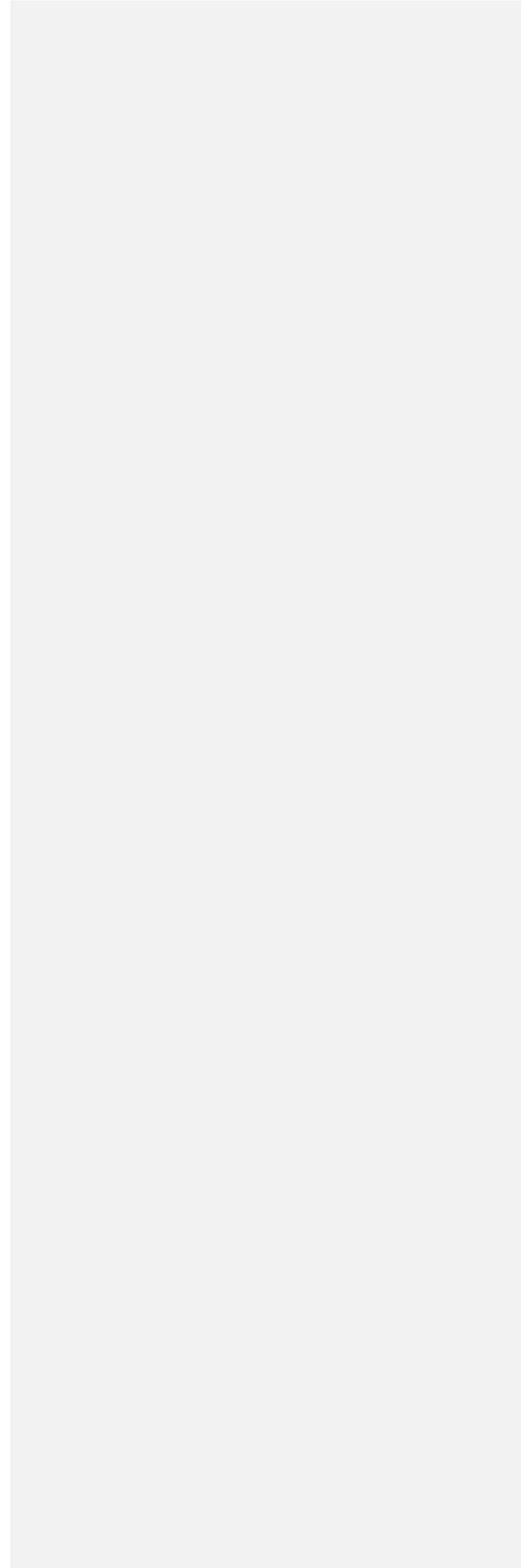
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**ABSTRACT**

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## INTRODUCTION

Cardiovascular diseases (CVD) are among the leading burdens of disease and disability globally<sup>1</sup>. Cardiac rehabilitation (CR) is a model of secondary prevention to mitigate this burden. It is comprised of specific core components such as structured exercise, risk factor management, patient education and psychosocial counseling<sup>2,3</sup>. Utilization of CR is associated with 25% lower cardiovascular mortality, 18% less hospitalization, and improved quality of life<sup>4</sup>, among other benefits.

Accordingly, CR is a recommendation in international CVD clinical practice guidelines. It is recommended for patients with acute coronary syndrome<sup>5,6,7</sup>, following revascularization procedures<sup>8,9</sup>, heart failure<sup>10,11</sup>, and in specific populations such as women with CVD<sup>12</sup>.

CR utilization is comprised of 4 elements (Figure 1)<sup>13</sup>. Patients must first be referred to CR by a healthcare provider. A Canadian Cardiovascular Society (CCS) – Canadian Association of Cardiovascular Prevention and Rehabilitation (CACPR) position statement regarding promoting CR referral is available elsewhere<sup>14</sup>. The patient-related aspects of CR utilization which are the focus of this policy position are three-fold: enrolment, adherence and completion (see definitions in Figure 1).

Although CR is strongly recommended after a cardiac event, its' use is suboptimal. CR utilization rates vary by jurisdiction, owing to multi-level factors<sup>15</sup>, and hence global utilization rates are not established. A meta-analysis of CR enrolment rates reported an overall rate of 42.3 ± 18.7% (median 39.3%)<sup>16</sup>, and of adherence of 66.5 ± 18.2% (median 72.5%) of prescribed sessions<sup>17</sup>.

With regard to enrolment, the largest and most recent cohort where this was assessed using administrative data was in the United States, where enrolment rates of 16.3% were

reported in Medicare beneficiaries post-myocardial infarction or revascularization<sup>18</sup>. Again, the only population-based data of which we are aware with verified adherence stems from the United States, and showed that 40% of Medicare beneficiaries attended  $\geq 30/36$  and 13% of included participants attended  $< 6$  of 36 prescribed sessions<sup>19</sup>. The ASPIRE-2-PREVENT study in 19 randomly-selected hospitals in the United Kingdom reported that while 70% were “advised” to attend, 52% of all patients self-reported attending half of prescribed sessions<sup>20</sup> (which is only on average about 10)<sup>21</sup>; EUROASPIRE IV which assessed cardiac patients from 78 hospitals across 24 European countries revealed that while 51% were advised to attend CR, 41% of all patients self-reported attending half of prescribed sessions<sup>22</sup> (these are likely over-estimates due to socially-desirable responding). Representative population-based data on completion rates are available in the United Kingdom’s CR registry; results suggest 77% of participants complete CR<sup>23</sup> (but caution is warranted in over-interpretation as sites may not enter data for patients who only attend an initial session). Utilization rates are even lower in non-high-income countries<sup>24</sup> where the epidemic of CVD is at its’ worst.

### **Rationale and Purpose**

Given the benefits of CR, benchmarks for utilization have been previously established. Indeed, the purpose of this policy statement is to provide guidance on interventions that will ensure these benchmarks are met. Specifically, the aim is that 70% of indicated patients enroll in CR<sup>14</sup> (given that some patients may have legitimate contraindications; see exclusions below), and that they participate in at least 12 sessions (although 36 sessions is associated with even better benefit)<sup>25</sup>. We ambitiously set a target of CR completion by 70% of enrollees.

The impact of achieving greater CR utilization are evident. For example, based on 2005 CR utilization rates post-MI in Ontario, Canada, it was projected that if CR use was increased to

a 90% benchmark, there would be 135 deaths prevented or postponed annually, with a 1.3% (95% CI, 1.0-1.6) reduction in CVD mortality<sup>26</sup>. In a study conducted in the United States, the number of deaths that could be delayed or postponed if “perfect” guideline-based care (e.g., revascularization, optimal medical therapy, CR) was provided following acute cardiac events was estimated. Out of 10 treatments of known effectiveness for myocardial infarction, other than acute revascularization, the greatest number of patient deaths could be prevented or postponed with optimal CR utilization. Similarly, optimal CR utilization was estimated to prevent or postpone the greatest number of deaths in patients with unstable angina and heart failure, compared with other guideline-based treatments<sup>27</sup>.

With regard to adherence, the dose-response relationship between CR use and outcomes has been well-established; the more sessions patients attend, the better their outcomes<sup>28,29</sup>. A recent review examining CR dose showed adherence to a minimum of 12 comprehensive CR sessions was associated with 42% reductions in all-cause mortality, and adherence to 36 sessions was associated with 35% reductions in revascularization (percutaneous coronary intervention)<sup>25</sup>. Finally, it is also well-established that CR completers have lower death rates than non-completers<sup>30</sup>.

Therefore, the objective of this policy position is to develop evidence-based recommendations on interventions to increase patient enrolment in, adherence to and completion of CR. The recommendations provided herein are directed to healthcare practitioners providing inpatient acute cardiac care (e.g., nurses, physiotherapists, pharmacists), any referring providers (e.g., cardiologist, cardiac surgeon, internist, family physicians), and CR providers. CR promotion interventions should be initiated in the inpatient setting, and also delivered during CR.

It is hoped these recommendations will increase CR referral vicariously, but primarily patient utilization of CR, which in turn should improve patient outcomes. Indeed, implementation of the recommendations and tools could result in significant public health benefit, such as reduced cardiovascular mortality, morbidity and re-hospitalization, as well as optimize role resumption and quality of life, and decrease healthcare costs.

## **METHODS**

### **Writing Panel Composition & Stakeholder Engagement**

The writing panel was constituted based on the process of the CACPR Guidelines Executive Committee, and with input of the International Council of Cardiovascular Prevention and Rehabilitation Executive Committee (ICCP). They recommended representatives of major CR societies (and where possible the corresponding authors of trials which were included in the Cochrane review<sup>31</sup> which forms the evidentiary basis for this policy statement were invited to represent their corresponding national CR association), while ensuring that the panel had diverse geographic representation, and included the healthcare provider types that would be implementing the recommendations (e.g., nurses, physiotherapists, among others). Panel co-chairs were approved by both committees (CSP, SLG).

Patient partners (JS, PM) were solicited to serve as well as policy-makers (AA, NZ, SC, BR, SB, AG) to ensure implementability and uptake of the recommendations. The World Health Organization and World Heart Federation were informed about the initiative, with a request for advice regarding implementation. A methodologist was secured (AG).

All members were required to disclose conflicts of interest, financial relationships or personal interests from 12 months before initiation of the writing effort that could impact their

contributions to this statement at the time of statement initiation. These were collated and reviewed on a web call of the writing panel. Finally, an external review panel was also populated, comprised of scientific and clinical experts, as well as representatives of relevant organizations and agencies.

### **Evidence collection, Grading criteria and Synthesis**

This position statement is based on the results of the Cochrane systematic review update with meta-analysis on interventions to promote patient utilization of CR undertaken by the co-chairs<sup>31</sup>. In brief, comprehensive literature searches were performed in July 2018 of 6 databases. The search strategy consisted of 4 elements: (1) Cardiovascular diseases, (2) Patient compliance (enrolment, adherence and completion outcomes), (3) Rehabilitation, (4) Motivational interventions and education.

Articles were included in the review if the following criteria were met: (i) included patients had a CR-qualifying condition, (ii) there was an intervention targeted to patients / groups, their partners / caregivers or other family members, or healthcare professionals with the specific aim of increasing patient utilization of phase 2 comprehensive CR, (iii) their design was randomized or quasi-randomized. Evidence for each outcome was evaluated according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system<sup>32</sup>.

### **Development Process**

Recommendations were initially developed by the panel co-chairs, in accordance with the Appraisal of Guidelines for Research and Evaluation (AGREE)-II<sup>33</sup> and National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS)<sup>34</sup>. Exclusions were also drafted for rating. The 3 drafted recommendations and exclusions were circulated to all other authors, who were asked to rate each on a 7-point Likert scale in terms of scientific acceptability,

actionability, and feasibility of assessment<sup>35</sup>. Additionally, overall comments were requested. The ratings and comments from the authors were collated anonymously and shared with authors. It was established a priori that recommendations with mean overall ratings  $<5/7$  would not be accepted as is<sup>36</sup>. A webcall was convened discuss areas where consensus was lacking (as per standard deviations below, there was very high consensus), revisions based on comments provided, and to confirm strength of the recommendations. The senior author chaired the call to ensure all perspectives were voiced. The recommendations were revised accordingly.

The policy statement outline was developed by the co-chairs as well. Benefits and harms of the recommendations were considered, as well as costs and implementability. The first draft of the policy position was circulated to the writing panel for input concurrent with the recommendations. Feedback was incorporated by the co-chairs. A written record of feedback and corresponding edits has been archived. The revised policy statement was circulated to the writing panel for discussion on the webcall, as well as to an independent external review panel of experts (see acknowledgments).

With integration of further input, it was submitted to the ICCPR Executive Committee and CACPR Guideline Executive for approval, and then to the major cardiac societies globally for endorsement consideration. The draft was also posted on ICCPR's website for a 45-day period to enable interested public stakeholders to provide input. Input received from associations and stakeholders was documented and considered, and integrated where appropriate. The writing panel will consider updating this position statement in accordance with updates to the corresponding Cochrane review, where changes to conclusions are found, new and superior interventions are identified or harms raised<sup>31</sup>.

## CR Utilization Recommendations

As outlined below, effective strategies to increase patient utilization of CR were identified for each indicator / outcome<sup>31</sup>. Therefore, all inpatient and outpatient settings as applicable treating CR-indicated patients should be implementing these strategies to promote utilization.

Recommendations are shown in Table 1. Overall ratings for the 3 recommendations were 5.96±0.68 (mean ± standard deviation), 5.33±1.12 and 5.64±1.08 on the 7-point scale respectively.

All authors of successful interventions (i.e., point estimate on right side of line of unity and confidence intervals did not cross) were contacted to request their materials used, along with their permission to post them open source for use in your setting. Received tools are available at

<http://www.yorku.ca/sgrace/crutilizationtools.html>.

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## Enrolment Strategies

The meta-analysis demonstrated that enrolment interventions resulted in 27% greater utilization than was observed with usual care<sup>31</sup>. Subgroup analyses revealed interventions were most successful if they targeted nurses (sometimes with peers or allied healthcare providers; no trials intervened with physicians), to deliver them face-to-face, although these were only trends (i.e.,  $p > .05$  but  $< .1$ ).

Successful interventions included: home visits and telephone calls<sup>37,38</sup> (including women-centered telephone calls<sup>39</sup>); coordination of the transfer of care between the hospital and general practice (where CR was provided)<sup>40</sup>; reducing the time to start CR (within 10 days)<sup>41</sup>; peer navigation (at the hospital bedside, then by phone or mail post-discharge; tools available online)<sup>42</sup>, text messaging<sup>43</sup>; and theoretically-based letters<sup>44</sup>.

### Adherence Strategies

The meta-analysis demonstrated that adherence interventions resulted in significantly greater utilization than was observed with usual care<sup>31</sup>. Successful interventions included: a gender-tailored CR program<sup>45</sup>; a brief program<sup>46</sup> (there may be bias here in that it would be easier for patients to adhere to fewer sessions, and it key that patients participate in a sufficient number of sessions to achieve the benefits); theoretically-based group<sup>47</sup> and individual (tool available online)<sup>48</sup> sessions; and exploitation of unsupervised settings<sup>49,50</sup>. Indeed, subgroup analyses revealed unsupervised delivery appears to be key, although this should be interpreted with caution as participation in a phone call is much easier for patients than attending a session on-site (i.e., low comparability of adherence operationalization).

### Completion Strategies

Again, the meta-analysis demonstrated that adherence interventions resulted 13% greater completion than is observed with usual care. Successful interventions included: theoretically-based patient education (tool available online)<sup>48</sup> and a smartphone-based intervention<sup>43</sup>. None of the subgroup analyses were significant.

## **LIMITATIONS**

The limitations of the evidence review are reported elsewhere<sup>31</sup>. Chiefly, the interventions evaluated were varied and often multifaceted, resulting in high heterogeneity.

## **IMPLEMENTATION CONSIDERATIONS**

## **Exclusions**

Endorsement of CR should be given to all indicated patients as per the guidelines cited in the introduction, however there are a few valid instances where CR is contraindicated (i.e., severe mental illness / cognitive disorders [e.g., schizophrenia, advanced dementia; but not depression], comorbid terminal illness / palliative care [e.g., non-curable cancer with expected life expectancy < 1 year], permanent resident in a long-term care facility). There can also be cardiac reasons that a patient may not be appropriate for the exercise portion of CR, but these patients should utilize all other core components (i.e., unstable angina, acute decompensated heart failure, cardiac infections, uncontrolled ventricular arrhythmias, aortic dissection, severe aortic stenosis, severe valvular regurgitation, acute thrombophlebitis, pulmonary or systemic embolism). These exclusions had an overall rating of 6.33/7. However, inability to ambulate (i.e., patient should receive non-exercise components; could use ergometer for upper extremity), lack of proficiency in the primary language in which the program is delivered (i.e., interpretation and translation services should be used), perceived lack of motivation (i.e., assuming patient would not be interested due to age or socioeconomic considerations) are not valid reasons to fail to promote CR utilization (overall rating 5.92/7).

## **Benefit-Harm Assessment**

No studies considered the potential harms associated with the interventions. It was suggested to offer CR in unsupervised settings; given the safety and comparable efficacy of CR in non-supervised settings has been well-established<sup>51</sup>, there should not be concern of harm. These exclusion criteria above should be considered when triaging patients to supervised or unsupervised settings; however most patients can safely be transitioned to unsupervised settings with standard risk assessment and following a few supervised sessions.

An observational study has suggested that offering too much reassurance and optimism to patients about their recovery during bedside discussions may be related to lower CR use<sup>52</sup>. In no trials were interventions associated with significantly lower utilization, however clearly consideration of messaging to patients is needed, balancing the need to reassure patients with the need to realistically convey what they can expect for their recovery. Ultimately, further research is needed on specific, optimal messaging to convey to patients to quell excessive anxiety yet promote CR utilization.

Overall, despite some null finding for all-cause mortality reductions in some recent CR meta-analyses<sup>4,53</sup>, CR is well established to be associated with many benefits (see introduction), and hence the potential harms associated with promoting utilization likely greatly outweigh any potential harms.

### **Value Judgments and Intentional Vagueness**

In terms of value judgments, again the authors perceive the benefits of CR are many, despite some recent null findings for the impact of CR in reducing all-cause mortality and revascularization<sup>4,53</sup>. Benefits for quality of life and re-hospitalization, among others, are not questioned in the literature.

Regarding intentional vagueness, its unknown whether specific tools used in the trials are generalizable to other settings, and hence specific tools or scripts have not been recommended. Replication of successful trial is needed, with an eye also to determining whether certain interventions are more effective and accepted in specific patient populations. Moreover, healthcare systems vary, in terms of inpatient length of stay, availability and reimbursement for

CR services, as well as types of providers interacting with patients, which could all impact which interventions may be more feasible and effective.

With regard to the latter, it is unclear what impact type of provider promoting CR would have on patient utilization as there are no trials comparing provider types; most involved nurses. It is assumed this physician discussion with patients has not been tested in a trial due to greater perceived time constraints, but data from observational studies suggests physician encouragement in particular greatly impacts patient utilization<sup>54,55</sup>.

### **Role of Patient Preferences**

Patients need to be aware of the existence of CR, and its' benefits. Intervention tools and scripts should be tailored to match patients' culture / language (i.e., translations, adaptations) and gender (i.e., consideration of women's unique needs)<sup>56</sup>, among other sociodemographic characteristics (e.g., socioeconomic status, rurality), and delivered in a patient-centered manner (i.e., make sure patients have sufficient time to ask questions about CR, and that their emotions related to recovery from a life-threatening cardiac event are validated and addressed)<sup>57</sup>. It may be helpful if the provider or peer discussing CR with patients is of a similar sex or ethnocultural background so they can understand some of the barriers patients may raise. Indeed, interventions to increase utilization should also take into consideration patient's barriers (e.g., transportation, return-to-work, costs)<sup>58</sup>. Where possible, informal caregivers should be involved in CR discussions.

Patient's emotional and cognitive state should also be considered. Many patients experience anxiety due to worry of repeat events, and CR is a setting where patients are monitored by clinical staff and are supported to feel more comfortable in resuming activities of

daily living. Moreover, approximately 20% of patients (even higher in heart failure) experience depression<sup>59</sup>. This can lead to low motivation, feelings of helplessness and psychomotor retardation – all factors which can impede CR participation but also be ameliorated by it. With regard to cognition, patients may have difficulty understanding and remembering discussions about CR if they have mild cognitive impairment (which may be temporarily caused by bypass surgery or cardiopulmonary resuscitation), have been sedated or are on medications which have cognitive effects, or dementia (depression can also impact cognition and decision-making). Provision of hard copy resources such as CR program flyers or cards with website information for patients to take home, and again inclusion of informal caregivers in referral discussions, could mitigate these cognitive issues.

Once referred, patients should be given the choice to attend a centre-based or home-based CR program based on their needs and preferences (including geographic barriers), particularly considering the results of the subgroup analysis showing adherence interventions are most effective when at least part of it is offered in an unsupervised setting (e.g., eCR). Patients electing home-based programs still need support (from peers and providers) to promote adherence.

### **Cost Implications**

In the one study that examined cost<sup>50</sup>, it was suggested that home-based CR may be more cost-effective than traditional supervised CR from a societal perspective. However, the Cochrane review in this area found equivalent costs of home versus supervised CR,<sup>51</sup> suggesting there is not likely an economic benefit associated with offering CR in alternative settings. Considering CR is demonstrated to be cost-effective when examined in multiple health systems<sup>60</sup>, even cost-saving considering avoidance of downstream healthcare utilization<sup>51</sup>, that even a few additional

CR sessions are associated with lower mortality<sup>61</sup> (and hence ability to contribute to society economically) and that CR participation is associated with return-to-work, clearly achievement of greater CR use overall has major benefits from a cost perspective.

No trial considered the cost of delivering a utilization intervention specifically. Given the nature of some of the interventions (e.g., healthcare providers making post-discharge home visits), these costs could be considerable, and should be quantified in future trials. These costs would substantially impact implementation in the real-world. Some tested interventions however could be particularly low-cost (e.g., motivational letter by Wyer et al., 2001)<sup>44</sup>, and hence could be scaled up across the cardiac population.

### **Capacity**

There are too few CR spaces in all countries of the world to provide care to all indicated patients<sup>62</sup>. The lack of capacity can result in referral failure by physicians. Where patients are still referred as per guideline recommendations, the result is long wait times to start CR; It is known that longer waits are associated with lower utilization and poorer outcomes<sup>63</sup>. Given the rise in technological capability and penetrance, alternative models (i.e., delivered remotely) such as eCR should be exploited to augment capacity (including early access to online education materials or capability to interact with peers online while on the queue; e.g., [cardiaccollege.ca](http://cardiaccollege.ca)). Integration of chronic disease management programs may also optimize resource utilization and hence augment capacity.

### **Potential Organizational Barriers to Applying the Recommendations**

In addition to capacity constraints within CR programs, limited human resources (staff availability, time) and financial resources could hamper implementation. Moreover, many

programs do not offer any, or have much, unsupervised CR capacity<sup>64</sup>. Some guidance is available on best practices in delivery of CR in these settings through ICCPR's certification program (<http://globalcardiacrehab.com/training-opportunities/certification/>).

### **Low-resource Settings**

The trials on which these recommendations were based were all conducted in high-income countries, and hence application to low and middle-income countries is unknown. Cardiac patients in low-resource settings have less access to both acute care (where they would be encouraged to enroll) and CR. Healthcare providers are often even more stretched in their responsibilities, leaving less opportunity for communication with patients about CR. Provision of written materials may be more feasible, but patient health literacy must be considered; use of peers or community healthcare workers to promote CR may be more feasible. On a related note, the type of healthcare providers referring to and delivering CR often differs, and hence the type of provider encouraging patients to utilize CR may not necessarily be a nurse. CR capacity is even more limited. ICCPR has developed recommendations regarding CR reimbursement advocacy<sup>65</sup> and on how to deliver CR in unsupervised settings<sup>66</sup>.

### **Implementation Tools**

As outlined above, the available tools used in the successful trials have been collated online. It is hoped that their availability will facilitate implementation of these recommendations. Moreover, there are quality indicators / performance measures on CR enrolment<sup>13,67,68</sup> adherence<sup>13,67,69</sup> and completion<sup>13,68-70</sup>. Adoption can facilitate assessment of whether utilization at your institution meets recommended benchmarks.

Finally, an online course was developed by the co-chairs to inform inpatient cardiac healthcare providers about the important role they play in promoting patient utilization of CR over-and-above referral, and providing tangible recommendations on how to encourage patients to enroll at the bedside. It informs healthcare providers about the nature of CR and the benefits of participation, which patients are eligible for CR utilization (and also that there are few contraindications), key talking points (i.e., describe CR, its' benefits, the reason for patient referral [i.e., it is recommended just like their medicines for heart patients], that they highly encourage their patient fully participate, and the enrolment process), as well as responses to some common barriers patients may raise (e.g., patients who live afar can access home-based programming; costs). It is applicable to all relevant provider types. It seeks to ensure providers' patients perceive they need CR, and that their providers strongly promote their participation. It is currently being evaluated, and if beneficial, will be disseminated more broadly.

## **RESEARCH DIRECTIONS**

Some interventions tested in the included trials were developed in an evidence-based manner and are grounded in theory, and some are available open source for future testing. Trials are needed to determine whether successful interventions can be replicated (with fidelity), and to establish generalizability as well.

Research is needed to establish and test simple, brief, specific talking points for providers and text for patients to encourage enrolment. This would be more amenable to translation and cross-cultural adaptation, which could have much broader application and impact. The impact of type of provider promoting CR referral also requires more investigation (with consideration of feasibility and cost).

There were no significant subgroup analyses for completion, which leaves little direction on how to augment this indicator. Surprisingly, delivery of CR unsupervised was not significant as it was for adherence. More research is needed in this area to identify approaches to augment program completion.

Finally, while overall CR utilization is sub-optimal there remain vulnerable populations who are often under-represented in CR. This includes patients of low socio-economic status, ethnoculturally-diverse, and “complex” patients (e.g., comorbidities, smokers). More trials are needed to establish whether offering gender-tailored CR is associated with increased utilization in women. There were some interventions targeted to older patients, but whether successful interventions work in these other under-represented groups warrants investigation, and if not, tailored interventions need to be developed and tested.

## **CONCLUSIONS**

CR utilization is sub-optimal, despite the established benefits. Interventions can significantly increase utilization of CR, and hence should be widely applied. Enrolment interventions should be delivered face-to-face by a nurse, and adherence is improved through remote delivery of CR. We call upon cardiac care institutions to implement these strategies to augment CR utilization, and to ensure CR programs are adequately resourced to serve enrolling patients and support them to complete programs.

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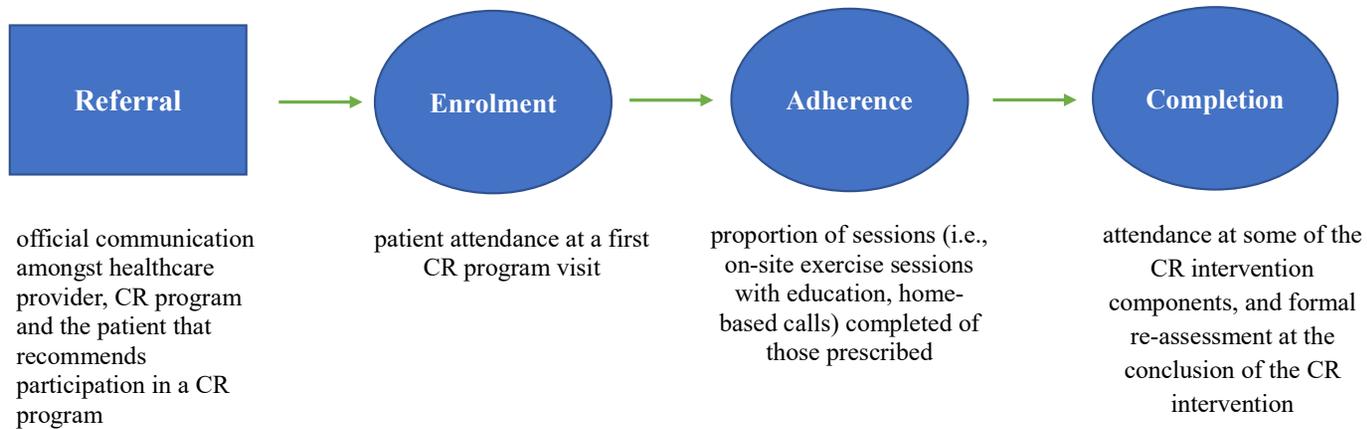
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FIGURE 1 – Definition of Cardiac Rehabilitation Utilization Indicators



CR = cardiac rehabilitation

Source: <sup>13</sup>

TABLE 1 –Recommendations for cardiac rehabilitation utilization interventions with level of evidence and evidence sources

Recommendation	Quality of the Evidence (GRADE)	Strength of the Recommendations	Evidentiary Basis
1. Interventions to increase CR enrolment should target healthcare providers, to impact delivery to indicated† patients	⊕⊕⊖⊖ LOW	Weak	Carroll et al., 2007 <sup>37</sup> ; Cossette et al., 2012 <sup>38</sup> ; Jolly et al., 1999 <sup>40</sup> ; Scott et al., 2013 <sup>42</sup>
2. Interventions to increase CR enrolment should be delivered face-to-face by a nurse, potentially in conjunction with an allied healthcare provider or peer.	⊕⊕⊖⊖ LOW	Strong	Carroll et al., 2007 <sup>37</sup> ; Cossette et al., 2012 <sup>38</sup> ; Jolly et al., 1999 <sup>40</sup> ; Price et al., 2012 <sup>39</sup>
3. To increase adherence, interventions should be delivered remotely or at least some of the cardiac rehabilitation program should be delivered unsupervised	⊕⊕⊕⊖ MODERATE	Weak	Focht et al., 2004 <sup>47</sup> ; Hwang et al., 2017 <sup>49</sup> ; Kraal et al., 2014 <sup>50</sup>

†acute coronary syndrome, revascularization, and heart failure, including women<sup>5,6,7,8,9,10,11,12.</sup>