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**A parallel-group, randomised controlled trial of a multi-media, self-directed, coping skills training intervention for patients with cancer and their partners: Design and rationale**

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## Article Summary

### Article focus

- Coping skills training interventions to promote patients' illness adjustment following a cancer diagnosis have been trialled, but equivalent research efforts to identify effective support for their partners are scarce, despite partners reporting as much if not more distress than patients.
- This study will examine the efficacy and cost-efficacy of a novel, evidence-based, multi-media, self-directed coping skills training intervention to empower patients and partners to manage the physical and psychosocial challenges posed by a cancer diagnosis.
- To the best of our knowledge, *Coping-Together* is the first intervention of its kind for couples adjusting to a recent cancer diagnosis.

### Key messages

- *Coping-Together* is an innovative coping skills training intervention that targets both patients and their partners, and translates current, evidence-based strategies for effective illness self-management and coping into a readily accessible format that couples can use where and when they need to.
- Over a 12 month period, this trial will directly examine the efficacy of *Coping-Together* in not only reducing negative psychological outcomes, but also on a range of outcomes known to impact patients' and partners' cancer experience (e.g., self-efficacy, dyadic coping).
- The self-directed format of this intervention has the potential to address issues of access to psychosocial support, especially for couples in non-metropolitan areas. In addition, the self-directed nature of *Coping-Together* means that it has the potential to be cost-effective and be integrated into practice without increasing pressures on the oncology workforce.

### Strengths and limitation

- Strengths include the projected sample size, recruitment from multiple sites across states, and the use of a longitudinal design. Also, *Coping-Together* covers a broad range of cancer-related challenges identified to be common unmet needs of couples facing cancer. The cost-efficacy of the intervention will be directly assessed in this trial, an important consideration as economic evaluation is an often overlooked element of intervention research.
- Challenges include the target population is vulnerable and experiencing an acute stressor that may impact on both recruitment and retention and the longitudinal nature of the design increases the likelihood of attrition.

## Abstract

**Introduction:** Coping skills training interventions have been found to be efficacious in helping both patients and their partners manage the physical and emotional challenges they face following a cancer diagnosis. However, many of these interventions are costly and not sustainable. To overcome these issues, a self-directed format is increasingly used. The efficacy of self-directed interventions for patients has been supported; however, no study has reported on the outcomes for their partners. This study will test the efficacy of *Coping-Together* – a multi-media, self-directed, coping skills training intervention for patients with cancer and their partners.

**Methods and analysis:** The proposed three-group, parallel, randomised controlled trial, will recruit patients diagnosed in the past 4 months with breast, prostate, colorectal cancer or melanoma through their treating clinician. Patients and their partners will be randomised to: 1) a minimal ethical care condition (MEC) – selected Cancer Council New South Wales booklets and a brochure for the Cancer Council Helpline, 2) *Coping-Together* generic – MEC materials, the six *Coping-Together* booklets and DVD, the Cancer Council Queensland relaxation audio CD, and login to the *Coping-Together* website, or 3) *Coping-Together* tailored - MEC materials, the *Coping-Together* DVD, the login to the website, and only those *Coping-Together* booklet sections that pertain to their direct concerns. Anxiety (primary outcome), distress, depression, dyadic adjustment, quality of life, illness or caregiving appraisal, self-efficacy, and dyadic and individual coping will be assessed before receiving the study material (i.e., baseline) and again at 3, 6, and 12 months post-baseline. Intention-to-treat and per protocol analysis will be conducted.

**Ethics and dissemination:** This study has been approved by the relevant local area health and University ethics committees. Study findings will not only be disseminated through peer-reviewed publications and conference presentations, but also through educational outreach visits, publication of lay research summaries in consumer newsletters, and publications targeting clinicians.

**Trial registration:** Australian New Zealand Clinical Trials Registry ACTRN12613000491763 (03/05/2013)

**Status of this trial:** recruiting

**Keywords:** psychosocial adjustment, couple, cancer, stress-coping, dyadic coping, anxiety, intervention, self-directed, information resources, economic evaluation

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2 Although substantial progress in the early detection and treatment of cancer means that the  
3  
4 five-year relative survival is now 66% for all cancers combined,<sup>1</sup> a cancer diagnosis is still appraised  
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6 as a life threatening illness and elicits greater distress than any other medical diagnosis.<sup>2</sup> From the  
7  
8 time of diagnosis and throughout treatment, patients and their partners contend with a wide range of  
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10 complex physical (e.g., treatment side effects), psychosocial (e.g., fear, uncertainty, anxiety), and  
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12 health care challenges.<sup>3-9</sup> The complexity of the situation is further heightened, as patients and  
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14 partners contend with any number of these challenges at the same time that they are also trying to  
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16 remain afloat with other life priorities.<sup>6</sup>  
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20 The difficulties experienced in managing cancer challenges are such that approximately a third  
21  
22 of patients experience high levels of physical or psychological distress,<sup>2 6 10 11</sup> with some studies  
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24 reporting comparable, if not higher, burden and distress among their partners.<sup>12-14</sup> This might in part  
25  
26 be attributed to partners' tendency to subjugate their own needs for those of the patient and to protect  
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28 patients from additional distress, often at the expense of their own emotional well-being. Although it  
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30 is generally assumed that elevated anxiety and depression are confined to the acute post-diagnosis, a  
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32 few studies have found that patients and partners experience chronic distress well into survivorship.<sup>15</sup>  
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34 <sup>16</sup> This is concerning as high distress has been associated with lower treatment adherence,<sup>17 18</sup> lower  
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36 quality of life,<sup>11 19 20</sup> higher incidence of cancer-related symptoms and side effects,<sup>21</sup> higher health  
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38 risk behaviours,<sup>17</sup> and reduced workplace productivity.<sup>22</sup>  
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45 Given the substantial burden of cancer, considerable research has focused on the impact of  
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47 patients' and partners' coping with cancer challenges on their health and well-being.<sup>14 23</sup> In their  
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49 seminal book on stress and coping, Lazarus and Folkman<sup>24</sup> defined coping as: *cognitive and*  
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51 *behavioural efforts to manage the demands of a situation or condition that is appraised as taxing or*  
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53 *exceeding the resources of the person.* Coping is typically characterised either as problem-focused  
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55 coping (alter the stressful situation using strategies such as information-seeking, planning and  
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57 problem solving) or emotion-focused coping (regulate situation-related emotions using strategies  
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2 such as positive reappraisal and behavioural disengagement) and further considered for their adaptive  
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4 versus maladaptive nature. The assumption is that if individuals use adaptive coping and are able to  
5  
6 regain a sense of control over cancer challenges and negative emotions, they are then less likely to  
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8 experience distress.<sup>25</sup> In this sense, coping is not only a valuable explanatory concept regarding  
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10 variability in response to stress, it can also serve as a portal for intervention, i.e., when adaptive  
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12 coping skills are not known, they can then be learnt.<sup>23 26</sup> Despite conflicting results, most studies  
13  
14 support the notion that increasing patient engagement with the stressor, through both problem- and  
15  
16 emotion-focused coping, is generally associated with more positive adjustment than when less  
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18 functional coping responses are used (e.g., avoidance, denial).<sup>13 25 26</sup> A number of studies have also  
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20 corroborated these findings among partners of individuals with cancer.<sup>14 27</sup>  
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27 Beyond individual approaches to coping, recent studies have further considered how patients  
28  
29 and partners interact as they attempt to cope together with cancer-related stressors and challenges  
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31 (termed dyadic coping).<sup>13 28 29</sup> The evidence on the impact of different dyadic coping strategies  
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33 mirrors to a certain extent that of individual coping, whereby adjustment is greater when patients and  
34  
35 partners respond to each other's stress, view cancer challenges as a shared problem, and engage in  
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37 joint problem solving that involves the pooling of resources.<sup>28 29</sup> Berg et al.<sup>28</sup> found that the  
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39 relationship between collaborative coping and illness adjustment for men diagnosed with prostate  
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41 cancer and their wives was partially moderated by heightened perceptions of coping effectiveness.  
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43 Conversely, when patients and/or partners use avoidant coping,<sup>13 30</sup> control<sup>30</sup> or protective buffering<sup>31</sup>  
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45 illness adjustment was compromised.  
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51 Based on the aforementioned evidence on individual and dyadic coping, considerable  
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53 intervention research efforts have focused on the development of coping skills training interventions  
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55 to maximise use of adaptive coping by patients and partners and so decrease physical and  
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57 psychological distress in response to cancer challenges.<sup>2 32</sup> Coping skills fostered by these  
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2 interventions typically include problem solving, symptom management, communication (with  
3 family/friends or health care professionals), and stress management. A number of reviews and meta-  
4 analyses have supported the efficacy of such multi-component, coping skills training interventions in  
5 decreasing patient and partner anxiety and increasing quality of life, particularly if these are based on  
6 principles of cognitive behaviour therapy.<sup>26 33</sup> Traditionally, these interventions have mainly focused  
7 on how patients cope with cancer-related challenges; however, with the increased recognition of the  
8 substantial burden of cancer on partners and the reciprocal relationship between partner's reactions to  
9 the cancer diagnosis,<sup>12</sup> coping skills training interventions are increasingly targeting both patients  
10 and partners as a unit.<sup>34</sup> Recent reviews have suggested that, in some contexts, couple-based  
11 interventions might be more efficacious in achieving optimal patient and partner adjustment than  
12 individual-based interventions.<sup>34 35 36</sup> This might in part be attributed to the shared learning that  
13 occurs in couple-based coping skills training interventions.<sup>34</sup>

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31 Although couple-based coping skills interventions seem promising for patients and/or their  
32 partners, issues pertaining to their accessibility and delivery linger.<sup>32</sup> Most coping interventions are  
33 labour intensive, requiring access to highly trained health care professionals, limiting their long-term  
34 sustainability due to high costs and problems with accessibility in rural and regional areas.  
35 Furthermore, there is evidence to suggest that conventional interventions may not be accessed by  
36 patients, due to personal preference, geographical barriers, and mobility issues.<sup>32 37 38</sup> One study  
37 found the uptake rate of referrals to psychosocial services by distressed patients to be as low as  
38 14%.<sup>39</sup> This suggests that service providers need to consider alternate approaches to ensure that the  
39 coping interventions for couples are not only efficacious and cost-effective, but also accessible and  
40 sustainable. Using a group format instead of an individual format has been proposed to address cost  
41 issues.<sup>40</sup> However, research has been equivocal regarding the suitability of these interventions in  
42 comparison to individual ones.<sup>40 41</sup> In addition, failure to create and sustain a functioning group is a  
43 challenge with some patient populations, which in turn might compromise the efficacy of the  
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2 intervention.<sup>40</sup> To overcome some of the challenges, whilst maintaining cost-effectiveness, the use of  
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4 a self-directed approach has been proposed.<sup>42</sup>  
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9 Self-directed (also termed self-help or self-administered) interventions address some of the  
10 issues surrounding access to face-to-face interventions and provide couples with greater flexibility in  
11 terms of when and how they engage with the intervention content. There is a growing body of  
12 evidence to suggest that self-directed coping skills training interventions are cost-effective and  
13 acceptable to patients.<sup>42-45</sup> Furthermore, research supports the efficacy of self-directed interventions  
14 for enhancing patient well-being,<sup>42-45</sup> especially for patients reporting elevated levels of distress<sup>44</sup> or  
15 high uncertainty.<sup>43</sup> Regrettably, all self-directed interventions reviewed to date are still mainly  
16 developed to directly address patients' concern, neglecting those of the partners. To address this gap  
17 in the literature our team has recently developed *Coping-Together*,<sup>46-48</sup> a self-directed coping skills  
18 training intervention for couples affected by cancer. This study will examine both the efficacy and  
19 cost-efficacy of this intervention.  
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### 33 34 35 **The *Coping-Together* Intervention** 36

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38 *Coping-Together* is an evidence-based, multi-media, self-directed coping skills training  
39 intervention to provide couples with the resources they need to confront the challenges posed by the  
40 cancer diagnosis and enhance their ability to cope with these.<sup>46-48</sup> *Coping-Together* takes a holistic  
41 approach to coping with cancer by addressing a range of common physical, social, and psychological  
42 challenges. The Medical Research Council framework for developing and evaluating complex  
43 interventions<sup>49</sup> was used to guide the development and evaluation of *Coping-Together*.  
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### 53 *Theoretical Underpinnings* 54

55 *Coping-Together* builds on three main theoretical frameworks:  
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- 1) Lazarus and Folkman's Stress and Coping framework,<sup>50</sup> which assumes that if individuals are able to cope and regain a sense of control over cancer challenges, they are then less likely to experience distress.
- 2) Bodenmann's framework of dyadic coping<sup>51</sup> extends Lazarus and Folkman's framework by acknowledging the reciprocal nature of stress and coping within couples and has become increasingly popular in the cancer literature.<sup>52</sup>
- 3) Bandura's self-efficacy theory, which posits that people are likely to engage in activities to the extent that they perceive themselves to be competent at those activities.<sup>53</sup> Individuals are postulated to achieve self-efficacy through various means, including performing a task successfully, witnessing other people successfully completing a task, being persuaded that one has the skills to succeed, and managing psychological responses that can adversely impact on how a person feels about their abilities in a particular situation.<sup>54</sup>

A detailed description of how each of these frameworks has guided the development of *Coping-Together* has been published elsewhere.<sup>48</sup>

### *Content*

*Coping-Together* encourages patients and their partners to try new skills and strategies demonstrated to be effective in helping couples: 1) manage symptoms and side effects, 2) forge a strong relationship with the health care team, 3) cope with treatment decision making, 4) locate additional support, 5) communicate about cancer, and 6) manage worries and emotions. These challenges were selected based on an initial perusal of the literature and content of existing couple-based interventions. *Coping-Together* collates the evidence on coping with these challenges and presents these as 'suggestions' to patients and partners across six booklets, a DVD, and a website.

For each key cancer challenge addressed by this intervention, the booklets focus on providing the following type of information: 1) social comparison information (testimonial and quotes from

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2 other patients and partners), 2) evidence-based, concrete ‘suggestions’ to manage the challenges, 3)  
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4 comments about the effectiveness of these strategies from others diagnosed with cancer, and 4)  
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6 empirical evidence supporting the coping ‘suggestion’. In addition, the booklets include several  
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8 behaviour therapy-based exercises, adapted from other self-directed coping skills interventions with  
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10 patients<sup>37 55</sup> or developed by experienced clinicians, and designed to encourage active learning. Table  
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12 1 summarises the content of each booklet. To ensure the accuracy of the information, the booklets  
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14 were reviewed by experts in the field, including clinicians and researchers, and the experts’  
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16 endorsement is included throughout each booklet.  
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20 INSERT TABLE 1 ABOUT HERE  
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25 The *Coping-Together* DVD features a clinician who delivers key content of the booklets and  
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27 includes scenarios with couples (actors) to demonstrate specific coping skills. The Cancer Council  
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29 Queensland relaxation CD is included to supplement the *Dealing with Stress and Worry* booklet.  
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31 Lastly, the *Coping-Together* website contains booklet and DVD content, complemented with  
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33 interactive features such as a question checklist generator, and tips for addressing common negative  
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35 thoughts. The website also contains an announcements page for communication postings by the  
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37 research team, contacts page for participants to communicate with the research team, and links to a  
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39 variety of credible information and support websites.  
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#### 44 45 *Feasibility testing of the Coping-Together booklets*

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47 A recent acceptability study of the *Coping-Together* booklets supported its self-directed  
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49 format and its practical approach. Patients’ and partners’ identified a number of benefits to using  
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51 these booklets, including increased awareness of challenges to prepare for, facilitated independent  
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53 coping, gave hope that something can help you “pull through”, provided a sense of normality,  
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55 connected patients and partners to people and services, and complemented support received from  
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57 health care professionals.<sup>46 47 56</sup> Many couples rated the booklets highly and the concrete coping  
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2 strategies described was a feature that set *Coping-Together* apart from other resources. Participants  
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4 also made particular comments on the appropriateness of the resource focusing on the couple, rather  
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6 than on the individual.  
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### 10 **Study Aims and Hypotheses**

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12 The *primary aim* of this study will be to assess the efficacy of *Coping-Together*, in  
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14 comparison to a minimal ethical care (MEC) condition, in decreasing anxiety in patients diagnosed  
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16 with breast, prostate or colorectal (bowel) cancer or melanoma and their partners at 3, 6, and 12  
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18 months post-baseline.  
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23 The *secondary aims* are to assess a) the efficacy of *Coping-Together* in comparison to the  
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25 MEC condition in decreasing distress and depression, and increasing positive illness appraisal or  
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27 caregiving appraisal, self-efficacy, quality of life, relationship satisfaction and positive individual  
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29 and dyadic coping at 3, 6, and 12 months post-baseline; b) the efficacy of generic *Coping-Together*  
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31 in comparison to a tailored version of *Coping-Together* in enhancing primary and secondary  
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33 outcomes over time; and c) cost-efficacy of *Coping-Together* in comparison to the MEC condition.  
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39 The *tertiary aim* is to explore moderators of outcomes, including distress, social support, self-  
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41 efficacy, information needs and preferences, and relevance and use of the material sent to address  
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43 challenges experienced.  
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### 47 *Hypotheses*

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50 ✓ Primary hypothesis: Significantly fewer *Coping-Together* participants will experience anxiety  
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52 at 3, 6, and 12 months post-baseline than MEC participants.  
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- ✓ Secondary hypotheses: a) From the health and broader societal perspective, *Coping-Together* (generic or tailored) will be more cost-efficacious than the MEC condition and b) *Coping-Together* participants will experience significantly less distress and depression and more positive illness or caregiving appraisal, self-efficacy, quality of life, relationship satisfaction and positive individual and dyadic coping at 3,6, and 12 months post-baseline than MEC participants.
  - ✓ Tertiary hypotheses: a) Couples in the tailored *Coping-Together* condition will report greater use of the resource and higher illness adjustment across primary and secondary outcomes than couples in the generic *Coping-Together* condition and b) the significant changes over time in anxiety among groups will be moderated by distress, social support, self-efficacy, information needs and preferences, resource use, and perceived relevance of the material sent to address the challenges experienced.

## 33 Methods/Design

### 34 Design

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The proposed study is a multicentre, stratified, double-blind, three-group, parallel, randomised controlled trial to compare generic *Coping-Together*, tailored *Coping-Together*, and the MEC condition (see Figure 1). The CONSORT statement<sup>57</sup> guided the design of this study.

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### 48 Sample and setting

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Patients will be recruited from participating private and public outpatient, multidisciplinary oncology clinics in Australia (Australian Capital Territory, New South Wales, South Australia, Western Australia, and Queensland). These clinics generally exist within large, general metropolitan or rural hospitals. Inclusion criteria are: a) patient recently diagnosed (within 4 months) with a primary, early stage breast, prostate, or colorectal (bowel) cancer or melanoma and receiving or

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2 planning to receive cancer treatment with curative intent, b) has a partner (spouse, boy/girlfriend or  
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4 de facto) who is also willing to participate in the study, c) patient or their partner scores  $\geq 4$  on the  
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6 Distress Thermometer (DT), and d) patient and partner are sufficiently fluent in English and  
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8 cognitively able to read study materials and complete surveys. Patient and partner consent is required  
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10 for the couple to participate in this trial. These inclusion criteria were selected to reflect current  
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12 recommendations for intervention studies in psycho-oncology, including targeting couples with  
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14 elevated levels of distress to avoid the potential for floor effect.<sup>58</sup>  
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### 20 **Sample size**

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22 Assuming that the standard deviation (SD) of patients' and partners' scores on the Hospital  
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24 Anxiety and Depression Scale-Anxiety subscale (HADS-A) is 4<sup>14 39</sup> and the correlation of baseline  
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26 and follow-up measurement is approximately 0.5, 133 couples per group will be sufficient to have  
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28 90% power to detect the minimal clinically significant difference of 1.5 on the HADS-A,<sup>59</sup> at the  
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30 2.5% significance level. This corresponds to over 80% power to detect a difference in the level of  
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32 anxiety between treatment groups at follow-up of 17% (e.g., 37% minimal ethical care versus 20%  
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34 *Coping-Together*). The 2.5% significance value is chosen to adjust for the multiple comparisons,  
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36 because the primary endpoint will be tested on the patient and partner separately. Assuming the  
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38 correlation between baseline and follow-up measurements of each of the secondary outcomes is  
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40 similar to that of anxiety, the study will have 90% power to detect a difference between treatment  
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42 groups of 0.375 SDs in each secondary outcome at the 2.5% significance level. In the unusual  
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44 situation where there is no correlation between baseline and follow-up values, the study will have  
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46 90% power to detect a difference of 0.438 SDs between groups at the 2.5% significance level. To  
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48 account for a 10% loss to follow-up at each time point,<sup>60</sup> 187 couples per group will be recruited at  
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50 baseline. Based on our most recent pilot,<sup>48</sup> it is estimated that recruitment will take 18 months.  
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### 58 **Procedures**

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2 Most participants will be referred to the study by their main treating clinicians, who will  
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4 identify patients meeting the medical and English fluency inclusion criteria, and briefly introduce the  
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6 study to patients, provide them with the study brochure, and obtain verbal or written consent to pass  
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8 on their contact information to the research team. The research team will then follow-up with  
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10 potential participants in approximately 1 week to confirm interest, further screen for their eligibility,  
11  
12 and mail a study pack to eligible participants. The study pack will include an information statement,  
13  
14 a consent form, and baseline survey and a study pack to pass on to their partner. Couples will then be  
15  
16 asked to return their consent forms and surveys, using the reply paid envelopes provided, with non-  
17  
18 responders followed-up, initially by mail and then by phone. Potential participants can refuse to  
19  
20 supply their contact details to their clinician and only take the brochure. Study participation will not  
21  
22 be further discussed with their health care team.  
23  
24

25  
26 Alternative recruitment strategies to cater to site specific requirements include having an on-  
27  
28 site research assistant (RA) to explain the study and provide the study pack or the referring clinician  
29  
30 may choose to mail invitation letters and study brochures to patients who meet the eligibility criteria.  
31  
32 The study will also be promoted by cancer care support organisations and through various media  
33  
34 facilities, including print (e.g., cancer care organisations consumer newsletters), radio, television and  
35  
36 online (e.g., Facebook). Interested individuals will also be able to contact the research team directly  
37  
38 for more information. Study posters and brochures will also be available at all recruitment sites. This  
39  
40 protocol has been approved by relevant local area health and University ethics committees.  
41  
42  
43  
44

#### 45 46 **Randomisation of group assignment**

47  
48 A computer-generated randomisation schedule with block lengths of variable size (6 or 9  
49  
50 couples) and stratified by cancer type will be programmed into a secure web-based randomisation  
51  
52 service, only accessible to the main project manager. Allocation concealment will be ensured, as the  
53  
54 website will not release the randomisation code until participants have returned their consent  
55  
56 forms/baseline surveys and their consent and information is entered into the secure website.  
57  
58  
59  
60

### ***Coping-Together* and Minimal Ethical Care Conditions**

At recruitment, participants will be informed that they will be mailed one of three packs: the generic *Coping-Together* pack, the tailored *Coping-Together* pack, or the MEC condition pack. All couples will receive their respective resource pack within 2 weeks of returning their baseline survey, and they will be informed that they can use any or all of these resources sent to them, at their own discretion and pace throughout the duration of the study.

*Blinding:* Participants are blinded to study hypotheses and group allocation, as they do not know which pack is the ‘study’ intervention, and the survey and contact with the research team are comparable across groups. Selected RA(s) will not be blinded to group allocation, and as part of their role will facilitate the randomisation of participants, assign participants identification numbers, and follow-up with participants in accordance with the protocol. The chief investigators and statisticians will remain blinded to group allocation until the database is locked.

*MEC condition:* A ‘no treatment’ control group will not be employed to ensure that participants are blinded to group allocation and because participants have reported elevated distress. Couples randomised to this condition will receive two booklets (cancer-specific and the ‘Caring for Someone with Cancer’ booklets) from the ‘Understanding Cancer Series’ available at the Cancer Council New South Wales along with a Cancer Council Helpline brochure. One to two weeks thereafter, a member of the research team will phone participants to orient them to the materials received (anticipated duration = 20 - 35 minutes).

*Generic Coping-Together:* Generic *Coping-Together* couples will receive the six *Coping-Together* booklets previously described, the *Coping-Together* DVD, a relaxation audio CD, and the login to the *Coping-Together* website. To ensure methodological equivalence of all groups, the generic



1  
2 *Coping-Together* group will also receive the relevant Cancer Council NSW booklets and Helpline  
3  
4 flyer (as per the MEC condition). One to two weeks thereafter, a member of the research team will  
5  
6 phone participants to orient them to *Coping-Together*. Then, monthly, couples will be mailed a 'Top  
7  
8 Tips' newsletter, featuring timely aspects of the booklets.  
9

10  
11  
12  
13 *Tailored Coping-Together*: Patients and partners randomised to the tailored *Coping-Together* group  
14  
15 will receive the log-in to the *Coping-Together* website and the DVD as well as an overview of the  
16  
17 topics addressed by the *Coping-Together* booklets; however, throughout the study, they will only  
18  
19 receive the *Coping-Together* booklet sections that pertain to their immediate concerns (main  
20  
21 difference between this condition and generic *Coping-Together*). The first pack will be created on the  
22  
23 basis of challenges identified by the baseline survey, and will also contain the relevant Cancer  
24  
25 Council NSW booklets and Helpline brochure (as per the MEC condition). Subsequent packs will be  
26  
27 tailored based on participant responses to the Cancer-Related Challenge Scale, sent monthly  
28  
29 throughout the study. Patients and partners might receive different tailored *Coping-Together*  
30  
31 materials. Couples in this group will receive the orientation call previously described in the MEC  
32  
33 condition. Couples in this group will receive the orientation call previously described in the MEC  
34  
35 condition.  
36  
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39

#### 40 **Data collection**

##### 41 *Initial distress screening with the Distress Thermometer (DT)*

42  
43  
44 The DT will ask participants to rate their overall distress in the past week using a visual  
45  
46 analogue scale ranging from 0= 'no distress' to 10= 'extreme distress'.<sup>17</sup> Since its publication, the  
47  
48 DT has quickly become the measure of choice for screening for distress, as it is short, simple to use,  
49  
50 and quick to interpret. To be eligible, either the patient or their partner must score 4 or above, which  
51  
52 is the recommended cut-off score on this measure.<sup>61 62</sup>  
53  
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57

##### 58 *Survey*

1  
2 A survey will be completed at baseline and at 3, 6, and 12 months post-baseline to measure  
3  
4 outcome variables, potential moderators, and socio-demographic and disease variables. Table 2  
5  
6 summarises all measures that will be used. The primary outcome (anxiety) will be measured using  
7  
8 the 7-item anxiety subscale of the Hospital Anxiety and Depression Scale,<sup>63</sup> the measure of choice to  
9  
10 detect anxiety among patients with cancer<sup>64 65</sup> and their partners.<sup>66</sup>  
11  
12

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14  
15 Secondary outcomes (distress, depression, illness or caregiving appraisal, self-efficacy, quality  
16  
17 of life, relationship satisfaction, individual and dyadic coping) will be measured by the DT,<sup>17</sup> the  
18  
19 Hospital Anxiety and Depression Scale depression subscale,<sup>63</sup> Kessler's Cognitive Appraisal of  
20  
21 Health Scale,<sup>67</sup> Mishel's Uncertainty in Illness Scale,<sup>68</sup> Caregiving Illness Appraisal Scale,<sup>69 70</sup> the  
22  
23 Communication and Attitudinal Self-Efficacy scale for cancer Scale,<sup>71</sup> Strategies Used by People to  
24  
25 Promote Health,<sup>72</sup> Health Education Impact Questionnaire (heiQ),<sup>73</sup> Caregiver Empowerment  
26  
27 Scale,<sup>74</sup> Assessment of Quality of Life (AQoL-8D),<sup>75</sup> Caregiver's QOL Index-Cancer,<sup>76</sup> Spanier  
28  
29 Dyadic Adjustment Scale,<sup>77</sup> the Brief COPE,<sup>78</sup> and the Dyadic Coping Inventory.<sup>79</sup>  
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35 Moderators will be measured at baseline and at 3, 6, and 12 months post-baseline, including:  
36  
37 unmet information needs (The Cancer Information Needs Survey – designed for the current study),  
38  
39 and social support (MOS-Social Support Survey<sup>80</sup>). Data pertaining to the use/relevance of the  
40  
41 resource, including coping skills learned, and information seeking preferences (The Profile of  
42  
43 Preferences for Cancer Information<sup>81 82</sup>) will be collected shortly after receipt of the resource  
44  
45 materials (first month), then again in the 3, 6 and 12 month follow-up surveys by the Resource  
46  
47 Evaluation Survey (Table 2). The main survey will also measure key socio-demographic, disease and  
48  
49 medical variables.  
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55 INSERT TABLE 2 ABOUT HERE

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### *Cost data*

For the purpose of the economic analysis, couples will be asked to provide consent for the research team to access their Medicare data (Australia's universal health insurance scheme). Additional questions regarding disruption to usual activities, hospital admissions, use of private allied health care services, use of community support services, and use of complementary/alternative therapies will be assessed in the baseline and follow-up surveys.

### *Orientation phone calls*

In addition, all couples (regardless of group allocation) will be contacted by a member of the study team for an initial orientation phone call, approximately one to two weeks after they receive their respective resource package. The intent of the orientation call is to ensure participants received the material, provide an overview of the content, and explore intended use of the resource. With participant consent, all phone calls will be audio recorded and coded to ascertain and monitor the topics that are discussed and as a quality check to ensure that counselling was not provided.

### **Strategies to enhance recruitment & minimise attrition**

Based on other couple-based intervention studies<sup>83</sup> and our pilot study,<sup>47</sup> the following strategies will be used to maximise recruitment and minimise attrition: 1) the study will be presented to the staff at each participating clinic to elicit support; 2) bright posters will be displayed in the clinics and an on-site RA will be present to facilitate recruitment; 3) couples will be approached at a time when the psychological aspects of their illness are more salient, thereby reinforcing psychosocial support as an important aspect of overall health;<sup>84</sup> 4) a self-directed intervention reduces participation burden, as participants can work through the materials at home and at their own pace; and 5) communication with the *Coping-Together* participants will be maintained for the duration of the study period to encourage attachment and completion (i.e., monthly 'Top Tip' newsletter).

## Data Management

All participant consent forms and surveys will be stored in a locked cabinet, as soon as logged by the project manager in the log and monitoring database. The data will be entered in a database specifically designed for this trial and by trained personnel. A random 10% of all data entry will be double-checked.

## Data Analysis

### *Analysis of primary and secondary outcomes*

Intention-to-treat and per protocol (i.e., patients and carers who used the intervention for most of the duration of the study) analysis will be conducted. The primary outcome, anxiety, will be measured repeatedly across time and, therefore analysed using generalised linear mixed models (GLMM). In this context, the GLMMs are similar to linear regression models, but take account of the correlation between repeated measurements on individuals. Sensitivity analysis will explore the robustness of the results against a range of missing data assumptions.<sup>85</sup> Separate analyses for patients and partners will examine differences between conditions in anxiety at 3 and 6 months. The outcome in the model will be the participants' scores at 3 and 6 months, the main predictor variable will be treatment group, and the participants' baseline score will be included as a covariate. Similar models will be used to determine if differences between groups are sustained to 12 months. GLMM will also be used to explore the secondary outcome measures. Multiple testings will be handled using the Benjamini and Hochberg method<sup>86</sup> with a nominal alpha set at .05.

### *Economic analysis*

This study will include a formal economic evaluation to assess the cost-efficacy of the intervention. The economic evaluation will comprise a cost-consequences analysis whereby the incremental costs of the intervention will be compared to the full spectrum of outcomes included in the study. This means that a series of cost-efficacy ratios will be determined rather than just one –

1 such an approach has been shown to be useful to decision-makers. The inclusion of the AQoL-8D<sup>75</sup>  
2 will also enable a cost-utility analysis to be undertaken whereby outcomes are expressed as generic  
3 quality-adjusted-life-years (QALYs). Outcomes expressed as QALYs have the advantage of allowing  
4 practical judgements regarding value for money credentials of the intervention to be made. The  
5 economic analysis will be largely from a societal perspective, although secondary analysis from  
6 narrower perspectives, such as health or government, will also be undertaken, as appropriate, to the  
7 different stakeholders of such a project. The actual costs of the interventions will be determined  
8 using information from the research team and provider records including interviews with key  
9 budgetary personnel to ensure all costs associated with the interventions have been captured. The  
10 Medicare data and information obtained during periodic follow-up surveys will be used to determine  
11 other resource use and costs incurred by patients and their partners.  
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27 The evaluation will first measure and value any change to the use of health care resources  
28 over the period of the study among the three arms of the trial and then compare any additional costs  
29 to the additional outcomes achieved. Standardised economic evaluation techniques including  
30 incremental analysis of mean differences, dominance analysis (where more than two interventions  
31 are compared) and bootstrapping to determine confidence intervals will be used in the evaluation.  
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#### 39 *Analysis of orientation calls*

40 All audio-recordings will be analysed by the interviewer using a summary data collection form  
41 to monitor the content of the orientation calls.  
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#### 48 **Ethics and Dissemination**

49 Minor adverse events (e.g., a participant being tearful and distressed during a session) will be  
50 logged and fed back to the study team by the end of the course. Serious adverse events (e.g.,  
51 expressing suicidal thoughts) will be reported immediately to the chief investigator and to the ethics  
52 committees. Any protocol amendments will be submitted to the ethics committees before these are  
53 implemented, and relevant changes will also be communicated to other relevant organisations (e.g.,  
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1  
2 trial registry). Study findings will not only be disseminated through peer-reviewed publications and  
3  
4 conference presentations, but also through educational outreach visits and interactive educational  
5  
6 meetings, publication of lay research summaries and recommendations for further actions in  
7  
8 consumer newsletters and websites, and publications targeting clinicians.  
9

## 10 11 12 13 **Discussion**

14  
15 *Coping-Together* is an innovative coping skills training intervention that translates evidence-  
16  
17 based strategies for effective illness self-management and coping into a readily accessible format that  
18  
19 couples can use where and when they need to. To the best of our knowledge, *Coping-Together* is the  
20  
21 first intervention of its kind for couples adjusting to a recent cancer diagnosis. Over a 12-month  
22  
23 period, we will investigate how *Coping-Together* is used by both patients and their partners to  
24  
25 address their main cancer-related challenges and examine how it impacts on the psychosocial  
26  
27 outcomes of patients and partners, with a focus on anxiety, depression, distress, coping, self-efficacy,  
28  
29 dyadic adjustment, and quality of life. The findings of this trial will add to the literature arguing for  
30  
31 greater psychosocial care in the acute post-diagnostic phase and early survivorship, while  
32  
33 simultaneously identifying both individual- and couple-level factors that contribute to patient and  
34  
35 partner outcomes.  
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42  
43 There are several strengths to this study and numerous potential benefits of the *Coping-*  
44  
45 *Together* resource that make it potentially an invaluable addition to the psychosocial care of couples  
46  
47 dealing with cancer. Firstly, the projected sample size, recruitment from multiple sites across states,  
48  
49 and the use of a longitudinal design will address some of the methodological limitations of previous  
50  
51 couple-based interventions in cancer care (e.g., being under powered).<sup>87</sup> Secondly, *Coping-Together*  
52  
53 covers a broad range of cancer-related challenges recently identified across three reviews as common  
54  
55 unmet needs of couples facing cancer. Specifically, the areas identified as requiring greater inclusion  
56  
57 in interventions that are covered by *Coping-Together* are strategies for communicating with health  
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1  
2 care professionals,<sup>7 87</sup> addressing communication difficulties between partners,<sup>7 88</sup> dealing with  
3  
4 emotional reactions such as fear, uncertainty, anxiety and depression in both partners,<sup>7 87 88</sup> and  
5  
6 learning new skills to overcome a lack of effective coping skills.<sup>87 88</sup> Thirdly, this trial will directly  
7  
8 examine the efficacy of *Coping-Together* in not only reducing negative psychological outcomes, but  
9  
10 also on a range of outcomes known to impact patients' and partners' cancer experience (e.g., self-  
11  
12 efficacy, dyadic coping). Fourthly, the self-directed format addresses issues of access to psychosocial  
13  
14 support, especially for couples in non-metropolitan areas. The use of multiple formats also  
15  
16 potentially increases the appeal of the resource, and therefore may increase utility to a broader  
17  
18 population of cancer patients and their partners. Finally, the self-directed nature of *Coping-Together*  
19  
20 means that it has the potential to be cost-effective and be integrated into practice without increasing  
21  
22 pressures on the oncology workforce. The cost-efficacy of the intervention will be directly assessed  
23  
24 in this trial, an important consideration as economic evaluation is an often overlooked element of  
25  
26 intervention research.<sup>89</sup>

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30  
31 Despite these strengths, there are also several challenges for the trial. The target population is  
32  
33 vulnerable and experiencing an acute stressor, which in turn may impact on both recruitment and  
34  
35 retention, a challenge identified by other trials with couples facing cancer.<sup>90</sup> Furthermore, the  
36  
37 longitudinal nature of the design increases the likelihood of attrition. An additional challenge is  
38  
39 whether the measures employed to assess change over time will be sensitive enough to detect  
40  
41 clinically significant improvements experienced by the couples.<sup>87</sup> This challenge is partly mitigated  
42  
43 by the integration of the Resource Evaluation Survey, which may help to clarify trends detected in  
44  
45 the outcome data.  
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**Competing interests**

The authors declare that they have no competing interests.

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The study detailed in this protocol is endorsed by the Psycho-oncology Co-operative Research Group (PoCoG), The University of Sydney, Australia. The study protocol and relevant documents have been reviewed by the PoCoG Scientific Advisory Committee and the Joint Community Advisory Group.

**Author's contribution**

SL conceived the study, participated in its design, led the development of the *Coping-Together* resource, and drafted the manuscript. AG, JT, JL, and KK participated in the design of this study, provided critical feedback on *Coping-Together*, and provided feedback on the draft of this manuscript. CM and PM developed the economic and statistical analysis plan for the study and provided feedback on the draft of this manuscript. SS and DB have critically reviewed all aspects of this study and the manuscript. All authors have read and approved the final manuscript.

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Table 1. *Coping-Together* booklet content

<i>Booklet title</i>	<i>Description</i>	<i>Example Challenges</i>	<i>Example Coping Strategies</i>
Getting What You Need From Your Health Care Team	Working with your medical team, knowing how to ask the right questions, getting and understanding the information you need	We don't know what questions to ask  We leave our appointments feeling we didn't get what we wanted	Use question checklists  Prepare for appointments, communicate assertively and use other methods of communication
Making Your Treatment Decision	Considering your options, treatment planning, and adjusting to treatment-related delays	We feel overwhelmed by options  We want more of a say in the decision	Identify what is most important to you, talk to your health care team and use decision aids  Use assertive communication and consider a second opinion
Getting on Top of Symptoms	Coping with common treatment side effects	Fatigue Pain	Use a symptom diary, talk to your health care team, and use self-care strategies
Dealing with Stress and Worry	Addressing the emotional reactions to diagnosis and treatment	I feel sad, down and/or isolated  I'm having difficulties sleeping	Do pleasant activities and connect with others  Practice good sleep hygiene throughout the day
Supporting Each Other	Enhancing your communication and connection to your partner, and adjusting to changes that may arise in your relationship	I just don't know how to make my partner feel better  I am stressed by changes in my roles and responsibilities	Use listening skills, body language and empathy, avoid roadblocks to listening well  Negotiate changes in roles and responsibilities and accept offers of help from others
Getting the Support You Need	Finding appropriate support to address practical, emotional, financial, legal, and informational needs	We need more information  We need legal help	Identify your information needs, identify the right source of information, check the information credibility and manage information overload  Identify the legal issues you need addressed and find a service that is right for you

Table 2. *Coping-Together* Study Outcomes and Measures

Outcomes	Measures and Psychometrics	
	Patients	Partners
<b>Primary Outcome</b>		
Anxiety	Main survey. 7-item HADS-Anxiety Subscale <sup>63</sup> ( $\alpha = .68-.93$ ) <sup>91</sup>	
<b>Secondary Outcome</b>		
Depression	Main survey. 7-item HADS Depression subscale <sup>63</sup> ( $\alpha = .68-.93$ ) <sup>91</sup>	
Distress	Main survey. Single item Distress Thermometer <sup>17</sup>	
Quality of life (QOL)	Main survey. 35-item Assessment of Quality of Life – 8 Dimensions Scale <sup>75</sup> (overall $\alpha = .91$ , subscale $\alpha = .64-.87$ ) <sup>92</sup>	Main survey. 35-item Assessment of Quality of Life – 8 Dimensions Scale <sup>75</sup> (overall $\alpha = .91$ , subscale $\alpha = .64-.87$ ) <sup>92</sup> Main survey. 35-item Caregiver's QOL Index-Cancer ( $\alpha = .91$ ) <sup>76</sup>
Relationship satisfaction	Main survey. 32-item Dyadic Adjustment scale (patients and partners) <sup>17</sup> ( $\alpha = .89-.95$ ) <sup>31</sup>	
Appraisal	Main survey. 28-item Kessler Cognitive Appraisal of Health Scale ( $\alpha > .70$ ) <sup>67</sup> Main survey. 33-item Mishel's Uncertainty scale ( $\alpha = .64-.91$ ) <sup>68</sup>	Main survey. 28-item Kessler Cognitive Appraisal of Health Scale [adapted] ( $\alpha > .70$ ) <sup>67</sup> Main survey. 33-item Mishel's Uncertainty scale ( $\alpha = .64-.91$ ) <sup>68</sup> Main survey. 27-item Appraisal of Caregiving Scale ( $\alpha > .85$ ) <sup>69 70</sup>
Self-efficacy	Main survey. 12-item Communication and Attitudinal Self-Efficacy Scale for cancer (CASE-Cancer; $\alpha = .76-.77$ ) <sup>71</sup> Main survey. 29-item Strategies Used by People to Promote Health (SUPPH, $\alpha = .76-.92$ ) <sup>72</sup> Main survey. 40-item Health Education Impact Questionnaire (heiQ, $\alpha = .70-.89$ ) <sup>73</sup>	Main survey. 12-item Communication and Attitudinal Self-Efficacy Scale for cancer (CASE-Cancer[adapted]; $\alpha = .76-.77$ ) <sup>71</sup> Main survey. 29-item Strategies Used by People to Promote Health (SUPPH, $\alpha = .76-.92$ ) <sup>72</sup> Main survey. 48-item Caregiver Empowerment Scale ( $\alpha = .76-.92$ ) <sup>74</sup> Main survey. 40-item Health Education Impact Questionnaire (adaptation, heiQ, $\alpha = .70-.89$ ) <sup>73</sup>
Dyadic and individual coping	Main survey. 37-item Dyadic Coping Inventory ( $\alpha = .73-.96$ ) <sup>79</sup> Main survey. 28-item Brief COPE measures 14 individual-level coping strategies ( $\alpha = .60-.90$ ) <sup>78</sup>	
<b>Moderators</b>		
Information-seeking preferences	Resource evaluation survey. 45-item Profile of Preferences for Cancer Information (PPCI) (adapted for partners) <sup>81 82</sup>	
Information needs	Main survey. 37-item Cancer Information Needs Survey	
Social support	Main survey. 19-item MOS Social Support Survey ( $\alpha = .91-.97$ ) <sup>80</sup>	
Cancer-related	Main survey (all groups) and monthly for the tailored group. 28-item Cancer-Related Challenge Scale, developed for use in the current study, aligns with the	

<b>challenges</b>	challenges presented in the Coping-Together intervention materials and will assist in assessing resource relevance.
<b>Use and relevance of Material sent</b>	<b>Resource evaluation survey.</b> Developed for use in the current study, and ascertains the extent to which participants used the material sent to them, including proportion of the material used and amount of time spent reading the material. Also examines the coping strategies learnt and the usefulness of the resource.
<b>Economic evaluation</b>	<b>Main survey.</b> 26-items developed for the current study assessing health service usage, hospital admissions, out-of-pocket expenses, medication usage, community and pastoral care services, disruption to work and usual activities.

### Figure legend

*Figure 1. Study design and groups*

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	ItemNo	Description	
<b>Administrative information</b>			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	<input checked="" type="checkbox"/>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	<input checked="" type="checkbox"/>
	2b	All items from the World Health Organization Trial Registration Data Set	<input checked="" type="checkbox"/>
Protocol version	3	Date and version identifier	Only version
Funding	4	Sources and types of financial, material, and other support	<input checked="" type="checkbox"/>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	<input checked="" type="checkbox"/>
	5b	Name and contact information for the trial sponsor	<input checked="" type="checkbox"/>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	No role
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A
<b>Introduction</b>			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	<input checked="" type="checkbox"/>
	6b	Explanation for choice of comparators	<input checked="" type="checkbox"/>

Objectives	7	Specific objectives or hypotheses	<input checked="" type="checkbox"/>
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	<input checked="" type="checkbox"/>
<b>Methods: Participants, interventions, and outcomes</b>			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	<input checked="" type="checkbox"/>
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	<input checked="" type="checkbox"/>
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	<input checked="" type="checkbox"/>
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	<input checked="" type="checkbox"/>
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	<input checked="" type="checkbox"/>
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	<input checked="" type="checkbox"/>
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	<input checked="" type="checkbox"/> Figure 1

1 2 3 4 5 6	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	<input checked="" type="checkbox"/>
7 8 9	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	<input checked="" type="checkbox"/>
10 11	<b>Methods: Assignment of interventions (for controlled trials)</b>			
12 13	Allocation:			
14 15 16 17 18 19 20 21 22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	<input checked="" type="checkbox"/>
23 24 25 26 27	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	<input checked="" type="checkbox"/>
28 29 30 31 32	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	<input checked="" type="checkbox"/>
33 34 35 36	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	<input checked="" type="checkbox"/>
37 38 39 40 41		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
42 43	<b>Methods: Data collection, management, and analysis</b>			
44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	<input checked="" type="checkbox"/>

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	<input checked="" type="checkbox"/>
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	<input checked="" type="checkbox"/>
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	<input checked="" type="checkbox"/>
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	<input checked="" type="checkbox"/>
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	<input checked="" type="checkbox"/>
<b>Methods: Monitoring</b>			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	<input checked="" type="checkbox"/>
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	<input checked="" type="checkbox"/>
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	<input checked="" type="checkbox"/>
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	<input checked="" type="checkbox"/>
<b>Ethics and dissemination</b>			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	<input checked="" type="checkbox"/>
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	<input checked="" type="checkbox"/>
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	<input checked="" type="checkbox"/>
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	<input checked="" type="checkbox"/>
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	<input checked="" type="checkbox"/>
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	<input checked="" type="checkbox"/>
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not included
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not included
<b>Appendices</b>			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included

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Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A
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For peer review only

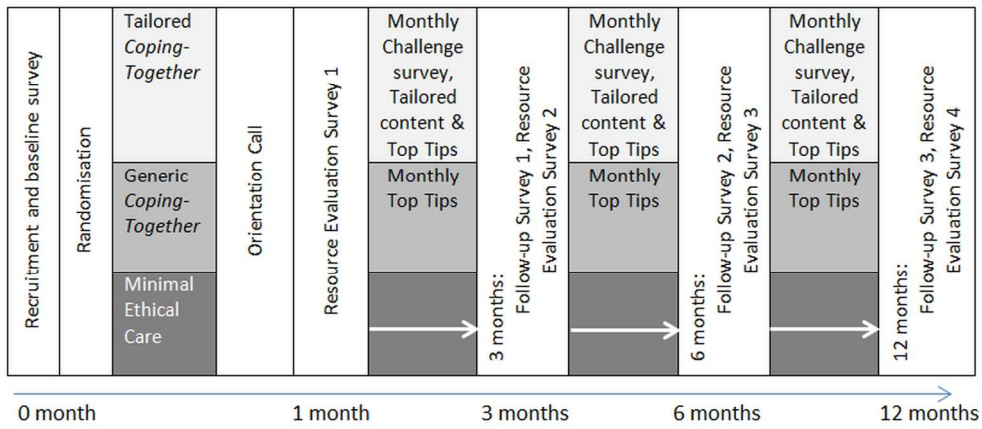


Figure 1. Study design and groups

190x90mm (300 x 300 DPI)

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