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1 **Title**

2 The impact of a self-administered coping intervention on emotional wellbeing in women
3 awaiting the outcome of IVF treatment: a randomised controlled trial.

4

5 **Running title**

6 Effect of a self-administered coping intervention

7

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22

23 **Running title**

24 Effect of a self-administered coping intervention

25

26 **Abstract**

27 **Study Question:** The aim of this study was to investigate the effect of the Positive
28 Reappraisal Coping Intervention (PRCI) on anxiety in women awaiting the outcome of an
29 IVF/ICSI cycle.

30 **Summary answer:** Women willing to participate in the RCT reported significantly more
31 anxiety during the waiting period than before treatment but the use of the PRCI did not
32 significantly reduce anxiety during the waiting period.

33 **What is known already:** Waiting for the outcome of IVF/ICSI treatment after embryo
34 transfer is one of the most stressful periods of fertility treatments. At present, no evidence-
35 based coping interventions are available to assist women through this waiting period. The
36 PRCI has been designed to address this unmet need by promoting positive reappraisal coping.

37 **Study design, size, duration:** A three-armed RCT evaluating the PRCI women undergoing
38 IVF/ICSI. Data were collected between October 2010 and June 2012. Participants were
39 randomised to receive either PRCI and emotional monitoring, emotional monitoring only, or
40 routine care. Only the PRCI-monitoring group received the coping intervention, comprising of
41 an explanatory leaflet and 10 statements to be read at least once in the morning and once in
42 the evening.

43 **Participant, materials, setting, methods:** To capture the general impact of the PRCI all three
44 groups completed questionnaires at three time points: just before the waiting period (Time 1:
45 stimulation phase), on day 10 of the 14-day waiting period (Time 2: waiting period) and 6
46 weeks after the start of the waiting period (Time 3: six-week follow-up). In addition, to
47 capture the specific impacts of PRCI on the days of the waiting period the PRCI-monitoring
48 and the monitoring-control group also rated daily, for the 14-day waiting period, their
49 emotions and reactions.

50 **Main results and the role of chance:** Three hundred and seventy seven of the women who
51 agreed to participate and met eligibility criteria were randomised. Study participants reported
52 significantly more anxiety and depression during the waiting period than before treatment (p
53 < 0.001). Mean difference in anxiety between time 1 versus time 2 was 1.465 (95%CI 1.098
54 to 1.832). Mean difference in depression between time 1 versus time 2 was: 0.514 (95%CI
55 0.215 to 0.813). Use of the PRCI did not significantly reduce anxiety or depression, or daily
56 negative emotions during the waiting period. However, patients randomised to PRCI reported
57 significantly more positive emotions during the waiting period ($p < 0.001$) than the monitoring-
58 control group, and reported the intervention to be easy to use, and as having a positive
59 psychological effect. No significant differences were found between groups in treatment
60 outcome.

61 **Limitations, reasons for caution:** The lack of difference observed in the present study
62 between the PRCI and the monitoring-control could have been due to the effects of
63 monitoring itself or its ability to attenuate or obscure effects of the PRCI intervention in
64 unknown ways. A randomised group of women that used only the PRCI without daily
65 monitoring would provide more insight.

66 **Wider implications of the findings:** The PRCI was shown to help women reinterpret the
67 demands of the waiting period in a more positive way. These results are consistent with
68 previous studies showing that positive reappraisal coping is a useful strategy for unpredictable
69 and uncontrollable situations represented by a medical waiting period. This simple low cost
70 self-help coping intervention increases positive affect during the waiting period in an
71 IVF/ICSI treatment.

72 **Study funding/competent interest(s):** The Women and Baby Division of the University
73 Medical Centre Utrecht funded the study. The authors have no conflicting interest(s).

74 **Trial registration number:** The study is registered at the Clinical Trials.gov (NCT01701011).

75

76 Key words

77 Coping-intervention, Medical waiting period, Randomised Controlled Trial, Anxiety, Positive
78 emotions

79

80 Introduction

81 In health-care patients often have to deal with different waiting periods that could be stressful
82 because the outcome of that period cannot be predicted or controlled, and is often difficult to
83 manage (Boivin and Lancaster, 2010; Lancaster and Boivin, 2008). Theory shows that patients
84 who are waiting for the results of medical treatments or examinations should use meaning-
85 based coping strategies to deal with negative anticipatory emotions (Folkman and Lazarus,
86 1988). Although medical waiting periods are stressful, research on coping interventions to
87 deal with waiting periods is limited (Phelps et al., 2012).

88 Meaning-based coping strategies can be helpful in situations that involve a prolonged period
89 of unpredictability and uncertainty. Tedlie Moskowitz et al. (1996) and Folkman and
90 Moskowitz (2000) observed that the use of the coping strategy positive reappraisal, by carers
91 of partners in the final stage of AIDS, led to positive emotions. People who use this strategy
92 try to reinterpret the meaning of the situation so that they can obtain some benefit. Folkman
93 and Lazarus (1988) suggested that the effect of positive emotions is to stimulate people to go
94 on in their efforts to deal with these enduring stressful situations.

95 Woman undergoing fertility treatment, cope with an unpredictable and uncontrollable waiting
96 period when they wait to find out whether or not treatment is successful. In a cross sectional
97 study among 242 women undergoing fertility treatment, ten significant difficulties were
98 identified like: monthly anticipation of treatment results (40%), lack of spontaneity in sexual
99 relationship (30%), uncertainty regarding the future (29%), not being able to solve the

100 problem myself (17%) (Benyamini et al., 2005). Research shows that the most stressful parts
101 of a fertility treatment are the waiting period after embryo transfer (ET), doing a pregnancy
102 test and finding out treatment was unsuccessful (Boivin and Takefman, 1995; Eugster and
103 Vingerhoets, 1999; Merari et al., 1992; Verhaak et al., 2010; Yong et al., 2000). Although
104 women have increased anxiety and depressive symptoms during the waiting period after ET
105 (Boivin and Lancaster, 2010; Eugster and Vingerhoets, 1999; Lancaster and Boivin, 2008;
106 Yong et al., 2000) they often do not look for psychological support (Boivin et al., 1999; Van
107 Dongen et al., 2012). Arguments for not searching for professional support are perceived
108 difficulty of scheduling sessions, not knowing who to contact and potential cost of sessions
109 (Boivin et al., 1999). This lack of action occurs despite the fact that women often wonder
110 whether stress influences the outcome of their fertility treatment. Meta-analyses make
111 conflicting conclusions about the role of stress with a lack of effect on single cycles (Boivin et
112 al., 2011) but possible effects on multiple cycles of treatment (Matthiesen et al., 2011).
113 Narrative and meta-analytic reviews about the impact of psychosocial interventions on
114 anxiety, depression and treatment outcome are also inconsistent (Boivin, 2003; Hammerli et
115 al., 2009). Inconsistency in these reviews could be due to the fact that psychosocial
116 interventions are generally aimed at the entire fertility treatment and not on a specific stage
117 like the waiting period after ET. A review found that psychosocial interventions in infertility
118 which emphasized education and skills training that focused on specific targets were more
119 effective than more general interventions which emphasized emotional expression and
120 support (Boivin, 2003).

121 The Positive Reappraisal Coping Intervention (PRCI) is designed for medical waiting periods
122 such as waiting for the outcome of a fertility treatment. The PRCI consists of a card with ten
123 statements and an information leaflet about the coping strategy which was designed to
124 stimulate the use of positive reappraisal coping. **The development of PRCI was in keeping**

125 with the Medical Research Council framework for development of complex interventions: it
126 used theory, integrated empirically validated determinants of behaviour, tested the
127 acceptability and feasibility of the intervention and estimated effect size for future randomised
128 controlled trials on effectiveness (Campbell et al., 2000; Craig et al., 2008). The development
129 of PRCI is described in detail elsewhere (Lancastle, 2006; Lancastle and Boivin, 2008) but is
130 briefly summarized here. Our goal was to develop a coping intervention that was theoretically
131 derived, simple enough for untrained patients to use by themselves (whenever needed),
132 sufficiently inexpensive to be made freely available, and generic so it could be adapted for
133 other health contexts.

134 From these considerations PRCI was conceptualized using the cognitive model of stress and
135 coping (Folkman, 1997; Folkman, 2011; Lazarus and Folkman, 1984) and the Velten positive
136 mood induction procedures (Velten, 1968). The first pilot study generated the potential pool
137 of statements for the PRCI card. Seventeen items with face validity as intervention items were
138 selected from three existing coping scales (COPE questionnaire, problem-appraisal coping
139 scale and Ways of Coping questionnaire). Two further items (“try to do something
140 meaningful” and “try to do something that makes me feel good”) were adapted from a
141 qualitative interview schedule designed to investigate the experience of positive meaningful
142 events (Folkman and Moskowitz, 2000). Seven filler items were also added, each of which
143 represented an alternative way of coping with stressful situations. In the first pilot study 36
144 patients waiting for assessment or treatment in the Accident and Emergency department were
145 provided with a hypothetical scenario of a patient waiting for important medical test results
146 and asked to imagine themselves in this situation and to rate (for all 26 selected reappraisal
147 and filler coping strategies) whether they would use the strategy, find it helpful, and capable
148 of making them feel more positive during this experience of waiting for important medical
149 test results. The analysis showed discriminant validity with the capacity of positive

150 reappraisal items to make the patient feel more positive in this situation rated higher than for
151 filler items (i.e., other coping strategies, ($t(35) = 2.13, p < .05$). As expected from theory, the
152 perceived helpfulness of the positive reappraisal items for this (unpredictable, uncontrollable)
153 medical waiting period was significantly higher than for the filler items (i.e., other coping
154 strategies). There was no gender difference in response to any items (all $ps < 0.05$) and
155 internal reliability amongst all positive reappraisal items was high (Cronbach alpha 0.89 for
156 beneficial ratings). Given these results, the final selection of the ten PRCI statements was
157 based on optimising percentage of patients endorsing use of the item, correlation with other
158 items, perceived helpfulness and potential for improved positive mood ratings. A second pilot
159 study was conducted to further model the intervention. In this study the psychological
160 wellbeing of medical students who used the PRCI ($n=19$) while they were waiting for seven
161 days to sit important exams was compared with a control group ($n=20$) who did not receive
162 the intervention. Students who received the PRCI read the card as instructed (twice per day on
163 average), felt more optimistic about their exam results in the last three days before the exam
164 and reported marginally fewer physical stress reactions (e.g., racing heart, sweaty palms). The
165 acceptability and feasibility of the PRCI was explored in an RCT of 82 women undergoing
166 IVF who were randomly assigned to PRCI, a positive mood induction (PMI) control group (“I
167 feel good”) or a daily monitoring control group. The RCT was additionally designed to
168 estimate effect sizes for PRCI effects on coping, appraisals and other psychological factors
169 related to the cognitive model of stress and coping (Lancastle, 2006). Women using PRCI
170 were found to appraise the waiting period as significantly more controllable ($F(2, 79)=3.10, p$
171 < 0.05) and reported significantly more challenge appraisals ($F(2, 79)=2.58, p < 0.05$) than
172 the positive mood induction group (Lancastle, 2006).

173 A feasibility study carried out in the Netherlands for the present study showed that 12/19
174 women (63%) undergoing IVF found the PRCI was suitable for this context and 17/19
175 (89.5%) rated PRCI as quick and easy (unpublished data).

176 These feasibility results suggest that PRCI could be useful for medical waiting periods and
177 that there would be sufficient interest among patients to make feasible a full RCT within the
178 two years available to do a trial. The aim of the present study was to investigate the effect of
179 the PRCI on emotional wellbeing in women awaiting the outcome of an IVF/ICSI cycle. The
180 primary outcome was general anxiety. Secondary outcomes were general depression,
181 treatment specific positive and negative emotions, evaluation of the intervention and
182 treatment outcome. It was hypothesised that PRCI would reduce general and treatment-
183 specific negative emotions in infertile women waiting for the outcome of their fertility
184 treatment compared to control conditions.

185

186 **Materials and methods**

187 **Trial design**

188 The PRCI was evaluated in a three-arm Randomised Controlled Trial (RCT). Participants
189 were randomised to a PRCI-monitoring group or to one of two control groups: monitoring-
190 control or routine care control group. To capture the general impact of the PRCI, all three
191 groups completed anxiety and depression questionnaires at three time points: just before the
192 waiting period (Time 1: pre-intervention), on Day 10 of the 14-day waiting period (Time 2:
193 waiting period intervention) and 6 weeks after the start of the waiting period (Time 3: post-
194 intervention). Mobile phone text reminders were sent to patients regarding completing the
195 Time 1 and Time 3 questionnaires (if necessary) and all patients received a reminder just prior
196 to the Time 2 assessment on the ninth day of the waiting period.

197 To capture the specific impacts of PRCI on the days of the waiting period, the PRCI-
198 monitoring and the monitoring-control group also rated daily, for the 14-day waiting period,
199 their treatment specific emotions and reactions. Daily monitoring has previously been shown
200 to be an efficient and sensitive way of evaluating emotional reactions during fertility
201 treatment, including the waiting period (Boivin and Takefman, 1995; Boivin and Lancaster,
202 2010) and to be sensitive to intervention effects during Assisted Reproductive Technologies
203 (ART) (de Klerk et al., 2005). One potential drawback of this method of assessment is that it
204 may impact on the reporting of emotions itself. For example, habituation or sensitisation to
205 monitoring per se may decrease or increase reporting of anxiety compared to groups that do
206 not monitor (Cohen et al., 1995). Due to this potential reactivity the monitoring-control group
207 also monitored emotions and reactions daily during the waiting period. The routine care
208 control group did not receive the intervention and did not monitor daily their reactions, but
209 completed questionnaires as per the other groups.

210

211 **Participants**

212 The RCT was conducted over a period of twenty months in a fertility clinic at a university
213 hospital in the Netherlands. The sample size calculation for the three-arm RCT was based on
214 the following parameters. To test the difference in psychological wellbeing between three
215 groups with a power of 95%, $\alpha=0.05$ and a medium effect size ($f=0.25$), a total of 297
216 participants was required (99 patients per group) (Polit and Hungler, 1999; Polit and Beck,
217 2008). Taking into account a 20% attrition rate at least 124 women had to be recruited in each
218 group. Effect size and attrition were derived from Lancaster and Boivin (2008). The inclusion
219 criteria were woman undergoing a stimulated or cryopreserved IVF/ICSI treatment cycle.
220 Women not speaking the Dutch language were excluded.

221

222 **Intervention and control group**

223 The PRCI-monitoring group received the PRCI. The PRCI is a small card that contains ten
224 positive reappraisal statements and a leaflet with a detailed explanation about this coping
225 approach. See Figure 1 for the PRCI card (contact author JB for complete intervention,
226 including PRCI leaflet). **Permission was obtained from Cardiff University to reproduce the**
227 **PRCI card**. The leaflet instructed women to read the PRCI at least twice a day, once in the
228 morning and once in the evening as well as at any other time they felt the need, and to think
229 about how each statement applied to them personally. The other groups did not receive the
230 PRCI.

231

232 **Materials**

233 Data were obtained with self-reported questionnaires, daily monitoring and from the medical
234 records. The following self-report measures were used:

235

236 The Background Information Form (BIF) is a 16-item self-report questionnaire designed to
237 obtain demographic (e.g. age, educational status), medical (e.g. previous illness) and
238 gynaecological (e.g. infertility diagnosis, previous infertility treatment) characteristics. This
239 form was completed by all groups pre-intervention (Time 1).

240

241 The Hospital Anxiety and Depression Scale (HADS) was used to measure general anxiety and
242 depression (Zigmond and Snaith, 1983). The HADS consists of 14 items (7 items for each
243 subscale) that are rated on a 4-point Likert scale. The total score is the sum of the 14 items,
244 and for each subscale the score is the sum of the respective seven items (ranging from 0–21).
245 Scores on each scale can be interpreted in ranges: normal (0-7), mild (8-10), moderate (11-14)

246 and severe (15-21) anxiety and depression. The Dutch version of the HADS has been shown
247 to be a valid and reliable instrument, including in the IVF/ICSI context (de Klerk et al., 2005).
248 All groups completed the HADS at Time 1, Time 2 and Time 3.

249
250 The Daily Record Keeping (DRK) form was used to rate positive and negative emotions daily
251 during the 14-day waiting period (PRCI-monitoring and monitoring-control groups only)
252 (Boivin and Takefman, 1995). The DRK was developed for use in fertility treatment and
253 comprises 46 possible reactions to the IVF waiting period, including the 20 positive and
254 negative emotions used in the present analysis. Women endorsed each of the reactions
255 provided on the DRK (e.g., happy, sad, anxious) according to whether, and to what extent,
256 they had felt that way in the previous 24 hours. Emotions were rated on a scale from 0 to 3,
257 with higher scores representing more emotion. These ratings were summed to compute
258 positive and negative emotion subscales that Folkman and Lazarus (1985) proposed to be the
259 emotional counterparts of particular appraisals of a situation. Negative emotions comprised
260 threat (e.g., tense, worried) or harm emotions (e.g., sad, discouraged) whereas positive
261 emotions referred to challenge (e.g., hopeful, positive) or benefit emotions (e.g., content,
262 happy) (Folkman and Lazarus, 1985).

263 The DRK has been used in numerous treatment studies with the Cronbach alpha for the
264 emotional subscale in the range of 0.76 to 0.82 for subscales (Boivin, 1997). The DRK item
265 on vaginal bleeding (i.e., spotting) was also used and was rated in the same way. This item
266 referred to light bleeding or spotting which occurs during the waiting period in approximately
267 30% of patients (De Sutter et al., 2006). Vaginal bleeding is not consistently associated with
268 pregnancy outcome (De Sutter et al., 2006) but may nevertheless affect daily emotional
269 reactions due to patient perceptions of the meaning of this symptom. The DRK was translated
270 and used in a Dutch study that showed good correspondence between the original and Dutch

271 version, and acceptable convergent and discriminant validity with other measures of anxiety
272 and depression (de Klerk et al., 2005). Participants were instructed to complete the DRK at
273 the end of the day and for the PRCI-monitoring-group at least one hour after reading the PRCI
274 card to limit the chance of DRK ratings being artificially and transiently influenced by
275 completing the DRK. The PRCI-monitoring and the monitoring-control groups completed the
276 DRK daily during the two-week waiting period from the day of ET until the day before the
277 pregnancy test. Women also noted on the DRK the number of times per day they read the
278 PRCI.

279
280 The Intervention evaluation form (IEF), a 23-item questionnaire developed to assess
281 perceptions of intervention, was used to assess PRCI in previous research (Lancastle and
282 Boivin, 2008). It measures the following aspects of the intervention: practicality (6 items),
283 acceptability (4 items), endorsement and feasibility (4 items), perceived psychological effects
284 (7 items) and perceived duration of intervention effects (2 items). The response scale varies
285 by item. The PRCI-monitoring group completed the intervention evaluation form at Time 2.

286
287 A medical chart review at the end of treatment was used to obtain data about treatment
288 outcome: clinical pregnancy and clinical pregnancy with fetal heartbeat. Clinical pregnancy is
289 a pregnancy diagnosed by ultrasonography of one or more gestational sacs or definitive
290 clinical signs of pregnancy (Zegers-Hochschild et al., 2009). Clinical pregnancy with fetal
291 heartbeat is a pregnancy diagnosed by ultrasonography or clinical documentation of at least
292 one fetal with heart beat (Zegers-Hochschild et al., 2009). The medical chart of all groups was
293 examined at six-weeks follow-up.

294

295 **Procedure**

296 The ethical committee of the University of Utrecht provided ethical review and approval for
297 this study. The opt-in method was used to recruit participants as per requirements of the
298 Ethics Committee. Participants were sent an invitation to the trial and if interested asked to
299 contact the research team using the reply form or email address provided. A researcher
300 contacted patients interested in the study to give more information about the study and answer
301 any questions. Those who decided to participate were sent a written information sheet and a
302 consent form to return in a pre-addressed stamped envelope. During their first visit to the
303 hospital, more information was given about the logistics of the study, as needed, but all
304 patients were given the same information according to a written protocol.

305 A computer-generated table of random numbers was used to achieve the stratified
306 randomisation of the 372 women who met the eligibility criteria. The type of treatment
307 (stimulated or with use of own cryopreserved embryos from a previous cycle) stratified the
308 population because emotions and expectations relative to a stimulated IVF/ICSI may differ
309 from a cryo-preserved treatment (Provoost et al., 2010; Svanberg et al., 2001). Randomisation
310 took place after the first assessment (Time 1: pre-intervention) between follicle aspiration and
311 ET. An independent researcher was responsible for the randomisation. Participants were not
312 told what intervention was being evaluated, whether it was the intervention card or
313 monitoring form or psychological questionnaires. The independent researcher had no contact
314 with participants after randomisation. All women received written information about group
315 assignment on the day of the ET. They received instructions for the waiting period in an
316 opaque sealed envelope after the ET. The clinical staff that performed the ET was blinded to
317 the content of the envelope. After the ET, there was no further contact between the clinical
318 staff, other patients, or the researcher during the 14-day waiting period. An independent
319 research assistant verified random data input for accuracy of the database.

320

321 **Statistical methods**

322 IBM SPSS Statistics 20 was used to perform the statistical analysis. Descriptive statistics for
323 means and standard deviations were used to describe baseline variables and outcome of the
324 intervention evaluation. Equivalence of baseline measures between groups was examined by
325 one-way analyses of variance (ANOVA) for normally distributed variables on interval or ratio
326 level and chi-square for variables on nominal level. If the groups were not comparable on
327 demographics, medical history, or gynaecological variables, those variables were employed as
328 covariates or factors in subsequent analyses. The onset of menstrual bleeding during the
329 waiting period could differ between women and therefore vaginal bleeding (i.e., spotting) was
330 used as a covariate in analyses. A mixed model for repeated measures was used to examine
331 the differences between the three groups over time for the primary outcome anxiety and
332 secondary outcomes depression and treatment-specific positive and negative emotions. All
333 models were estimated by the method of restricted maximum likelihood (REML) and the
334 Compound Symmetry covariance structure was chosen for the repeated measures. For the
335 DRK analysis, with 14 repeated measures, we used time as a continuous variable with a linear
336 contrast. **The parameter of the convergence criteria was set at 0.000001(absolute).** Results for
337 this outcome will be presented as slope over time and differences in slope between groups
338 when a group by time interaction is analysed. The analysis was performed according to
339 intention to treat. The main effect of time indicated change over time (regardless of group),
340 the main effect of group indicated overall differences between groups (regardless of time) and
341 the group by time interaction indicated differences between groups at each time point. One
342 sample t-tests were used to test whether evaluations of the intervention within the PRCI-
343 monitoring group were significantly different from the 'no effect' rating.

344

345 **Results**

346 **Recruitment, participant flow and baseline data**

347 Figure 2 shows the study flow chart. In the 20 months of recruitment, between October 2010
348 and June 2012, 1445 letters were sent to women with an invitation to the trial. Of the 565
349 women who replied via a letter or email, 188 (33%) were not eligible. See Figure 2 for the
350 main reasons of non-eligibility. The remaining 377 women were randomised and the 349 who
351 had an embryo to transfer (n=119 PRCI-monitoring, n=117 monitoring-control, n=113 routine
352 care control) received an opaque sealed envelope after transfer with detailed instructions of
353 the study procedures during the waiting period. The number of questionnaires returned at
354 Time 2 was 79% (n=100) in PRCI-monitoring, 90% (n=114) in monitoring-control and 82%
355 (n=102) in routine care control. The number of questionnaires returned at Time 3 was 72%
356 (n=92) in PRCI-monitoring, 81% (n=102) in monitoring- control and 73% (n=90) in routine
357 care control group.

358 Baseline characteristics of the participants are shown in Table I. The three randomised groups
359 were similar on these baseline characteristics except previous use of counselling for infertility,
360 which was more frequent ($p=0.009$) in the PRCI-monitoring (21.4%) and monitoring-control
361 groups (27%) than in the routine care control group (11.3%). This variable was used as a
362 covariate in subsequent analyses. Participants were also similar on highest education
363 achieved, duration of fertility treatment, child with current partner, child with previous
364 partner, other medical problems, previous experience of miscarriage, abortion, ectopic
365 pregnancy, stillbirth and perinatal death.

366

367 **Outcomes**

368 **All women used the PRCI. Women read the PRCI on average twice a day with a mean of 1.97**
369 **(SD: 0.63) and a range from 0.29-4.50. The percentage of women who read PRCI between 1**

370 and twice per day was 47.5%. The percentage of women who read PRCI twice or more a day
371 was 52.5%.

372

373 **General anxiety**

374 The final model had a random intercept for subject and fixed effects for groups and time with
375 adjustment for the baseline variable previous counselling for infertility and baseline anxiety.

376 For the models for Anxiety and Depression, respectively 4.9% and 4.2% of the studentised
377 residuals were outside the -2 to +2 range. Further, the maximum Restricted Likelihood

378 Distance (ranged 1.0 and 1.3) and the covratio (0.80 to 1.10 and 0.70 to 1.10 for Anxiety and
379 Depression respectively), all indicated no influential observations. The results for HADS-A

380 anxiety indicate a significant main effect of time ($F(2, 670)=47.37, p=0.000$), but no

381 significant main effect for group ($F(2, 373)=2.09, p=0.125$) or group by time interaction (F

382 $(4, 670)=1.79, p=0.129$). The contrast for the significant main effect of time revealed that for

383 all groups the anxiety level was significantly higher during Time 2 (waiting period

384 intervention), than Time 1 (pre-intervention) or Time 3 (post-intervention) (see Figure 3). The

385 mean difference between time 1 versus time 2 was: 1.465 (95%CI 1.098 to 1.832). The mean

386 difference between time 2 versus time 3 was: -1.783 (95%CI -2.175 to -1.392).

387

388 **General depression**

389 The final model had a random intercept for subject and fixed effects for groups and time with
390 the adjustment for the baseline variables previous counselling for infertility and baseline

391 depression. The results for HADS-D depression indicate a significant effect of time ($F(2,$

392 $673)=7.04, p=0.001$) but no significant main effect for group ($F(2, 379)=0.32, p=0.728$) or

393 group by time interaction ($F(4, 673)=1.38, p=0.241$). Contrasts for the significant main effect

394 of time revealed that the depression score was significantly lower at Time 1 (pre-

395 intervention), compared to Time 2 (waiting period intervention) and Time 3 (post-intervention
396 (see Figure 4). The mean difference between time 1 versus time 2 was 0.514 (95%CI 0.215 to
397 0.813). The mean difference between time 1 versus time 3 was 0.457 (95%CI 0.148 to 0.766).

398

399 **Treatment-specific negative and positive emotions**

400 The final model for the daily monitoring data had a random effect for subjects and fixed
401 effects for groups and time with adjustment for vaginal bleeding (spotting). **Influential**
402 **observations for the final models were identified through the distribution of studentised**
403 **conditional residuals. Only 4.2% of these residuals were outside the -2 to +2 range both in the**
404 **models for both positive and negative affect. Further, the maximum Restricted Likelihood**
405 **Distance (1.25 and 1.7) and the covratio (0.90 to 1.15 and 0.85 to 1.10 for positive and**
406 **negative affect respectively), all indicated no influential observations.**

407 Results for the DRK positive emotions indicated a significant main effect of time ($F(1,$
408 $2669)=322.06, p=0.000$) and a significant group by time interaction ($F(1, 2652)=16.15,$
409 $p=0.000$) with a non-significant group main effect ($F(1, 285) = 1.44, p=0.231$). The
410 significant main effect of time showed that the overall slope of positive emotions per day
411 was -0.041 (95% CI -0.046 to -0.037) and the significant group by time interaction showed
412 that the slope of positive emotions per day in the PRCI-monitoring group was higher (0.016,
413 95% CI 0.008 to 0.024) than in monitoring-control group.

414 Results for the DRK negative emotions for the two groups indicated a significant main effect
415 of time ($F(1, 2672)=73.93, p=0.000$) but no significant main effect of group ($F(1, 292)=1.17,$
416 $p=0.281$) or group by time interaction ($F(1, 2655)=3.38, p=0.066$). The significant time effect
417 showed the slope of negative emotions per day was 0.018 (95% CI 0.014 to 0.022). See
418 Figure 5.

419

420 **Intervention evaluation**

421 Women perceived that the stress of waiting would have been significantly higher without
422 PRCI: mean (SD): 7.04 (2.27), then with PRCI, 6.27 (2.05), PRCI ($t(101)=-7.20, p=0.000$).
423 Other aspects of the acceptability, feasibility and perceived helpfulness and benefits of PRCI
424 were all significantly different from the ‘no effect’ point on the item response scale (all $P_s <$
425 0.001). The effect of reading the PRCI was rated as lasting ≤ 20 minutes by 64.4%, mean
426 (SD): 1.62 (1.02), which on average women perceived as long enough, 3.04 (1.41). PRCI was
427 rated as helpful, 3.54 (1.26) and women would use it again, 3.73 (1.56), recommend it to
428 friends, 4.01 (1.34) or recommend it for other medical waiting periods (e.g., genetic testing),
429 3.66 (1.22). Furthermore the psychological effect of the PRCI was perceived to be in helping
430 to see things more positively, mean (SD): 4.78 (0.93), feeling more positive, 3.40 (1.34), and
431 sustaining coping, 3.05 (1.45). PRCI was less perceived to be a distraction, 2.89 (1.60), and
432 helping in making future plans, 2.36 (1.47).

433 Practicality was good. PRCI was rated as suitable, mean (SD): 3.97 (1.25), for the waiting
434 period, quick, 4.61 (1.18), and easy, 4.81 (1.07), to use. PRCI fitted in with the daily routine,
435 4.55 (1.19), and was not perceived to be a hassle to read, 1.89 (1.23). Women could memorise
436 statements, mean (SD): 3.73 (1.31), but thought it was difficult to remember to read the card,
437 3.08 (1.61).

438

439 **Treatment outcome**

440 No significant differences were found between groups on clinical pregnancy ($p=0.83$) and
441 clinical pregnancy with heartbeat ($p=0.76$) (see Table II).

442

443 **Discussion**

444 Waiting for the outcome of an IVF/ICSI treatment cycle was stressful with anxiety and
445 depression levels during the waiting period significantly higher than before treatment. Women
446 who used the PRCI intervention during the waiting period of IVF/ICSI reported significantly
447 more positive affect but not significantly less anxiety, depression or negative treatment-
448 specific emotions. Nevertheless, women evaluated the PRCI as acceptable, practical and they
449 perceived a psychological benefit to its use. PRCI had no effect on treatment outcome.
450 Overall, the pattern of results suggests that the main impact of PRCI was to make the stress of
451 the waiting period seem more tolerable rather than in taking away the negative emotions
452 waiting produces. This simple low cost self-help coping intervention can be offered to women
453 to increase positive affect during the waiting period of fertility treatment.

454
455 Waiting for the outcome of treatment was perceived to be stressful and was associated with an
456 increase in general anxiety and depression and negative emotions specific to treatment. These
457 results are consistent with those of numerous studies on ART (Boivin and Takefman, 1995;
458 Boivin and Takefman, 1996; Yong et al. 2000) that show that women appraise the waiting
459 period as a potential threat and as causing related anticipatory negative emotions (e.g.,
460 feelings of worry, tension, nervousness). According to cognitive stress theory, the factors that
461 make waiting periods stressful are the unpredictability and uncontrollability of the outcome
462 (Lazarus and Folkman, 1984). Rumination about the outcome arrests the coping process
463 because coping strategies would differ depending on whether one outcome (pregnant) or the
464 other outcome (not pregnant) was most likely (Lancastle and Boivin , 2008). These results
465 reinforce the need for effective coping interventions that help women manage the strains of
466 medical waiting periods, such as waiting for the pregnancy test in IVF.

467

468 PRCI produced the effects for which it was designed, namely to help women reinterpret the
469 demands of the waiting period in a more positive way. Women who used PRCI reported
470 significantly more positive emotions (e.g., encouraged, content, confident) during the waiting
471 period than did women assigned to the control group. In addition, patients perceived PRCI to
472 have benefit in helping to manage the stress of fertility treatment, even though PRCI use was
473 not associated with a significant reduction in negative emotional reactions (general or
474 treatment-specific). **The generation of challenge emotions (encouraged, confident) is in line
475 with original development data that showed that women using PRCI made more challenge
476 appraisals and perceived the waiting period as more controllable than women using a control
477 intervention (Lancastle, 2006). We have collected further data (to be reported separately) on
478 the effects of PRCI that shows that PRCI is associated with a greater use of positive
479 reappraisal coping compared to the controls groups. Our results support other research
480 showing that positive reappraisal coping is a useful strategy for unpredictable and
481 uncontrollable situations like the medical waiting period (Boivin and Lancastle, 2010).
482 Fredrickson (1998) proposes that positive affect can undo the after-effects of negative
483 emotions. Positive affect may restore autonomic inertness following negative emotional
484 arousal (Fredrickson, 1998). According to Folkman (2011) positive reappraisal and the
485 positive emotions it produces, can allow “psychological respite” during the waiting period,
486 which helps sustain coping during stressful situations. It should be noted too that the PRCI
487 items although originally culled from positive reappraisal measures such as the ways of
488 coping and COPE questionnaire may also tap into other related forms of meaning-based
489 coping (e.g., benefit-finding). **Future research needs to consider the extent to which cognitive
490 efforts to redefine the situation and/or derive benefit act synergistically or independently to
491 generate psychological benefits in uncontrollable and unpredictable situations like the waiting
492 period.****

493

494 We expected that the beneficial effects of PRCI (i.e., generation of positive emotions,
495 perceptions of helpfulness) would reduce the burden of waiting. However, women using
496 PRCI did not report lower day-to-day negative emotions during the waiting period (anxiety,
497 tension, nervousness), or lower general anxiety and depression during and after treatment.

498 Why the intervention only had an effect on positive affect is unclear but there could be a few
499 explanations. There is still an on-going debate about the importance of positive and negative
500 affect, and how they relate to each other (Folkman and Moskowitz, 2000; Folkman 2011).

501 The results of the present study indicate that feeling positive does not necessarily mean one
502 feels less negative. Cognitive reappraisal may play a more definite role in the ability to
503 regulate positive emotions whereas other types of coping (e.g., distraction, acceptance) may
504 be more central in the regulation of negative affect and symptoms of anxiety and depression
505 (Andreotti et al., 2013). The results suggest that interventions may need to comprise multiple
506 modes of coping beside positive reappraisal to help women deal with anxiety and depression
507 during treatment.

508

509 Research has demonstrated that positive affect is associated with better physical health and
510 lower risk of mortality, independent of negative affect (Folkman and Moskowitz, 2000;
511 Folkman, 2011). However, in the present study the use of PRCI was not associated with any
512 advantage for treatment outcome. This result is consistent with another study that showed that
513 positive affect was not related to pregnancy rates in fertility treatment (de Klerk et al., 2008)
514 but inconsistent with a study that found that enhanced positive affect was associated with
515 lower probability of failed treatment in IVF (Klonoff-Cohen et al., 2001). Our study differs
516 from the prospective study of Klonoff-Cohen et al. (2001) in the eligibility criteria and the
517 questionnaires and time points used for measuring positive affect. Past reviews and meta-

518 analytic studies on the impact of psychosocial interventions on treatment outcome are
519 inconsistent (Boivin, 2003 ; de Liz and Strauss, 2005; Hammerli et al., 2009). Further our
520 sample size calculation was not based on effect sizes for treatment outcome and therefore may
521 be underpowered for this outcome.

522

523 The results need to be considered in light of the strengths and limitations which should also be
524 considered for future evaluations of the PRCI tool. Feasibility studies had previously been
525 carried out to determine key uncertainties like attrition, recruitment, effect size, acceptability
526 and compliance of the intervention in the present (Lancastle, 2006; Lancastle and Boivin,
527 2008). Attrition was 20% (at Time 2), similar to that observed in previous studies (Lancastle
528 and Boivin, 2008) but was about 30% at Time 3. The use of mixed or multilevel modelling
529 (MLM) allowed analysis of partial response whilst maintaining power (Hoffman and Rovine,
530 2007). However, maximum likelihood estimation has been shown to provide unbiased and
531 efficient estimates only when the data are missing at random (Hoffman and Rovine, 2007).

532 We contend this to be the case but it is possible that attrition was due to some unknown
533 systematic cause. **An important aspect of intervention evaluation is to ensure that the
534 intervention is delivered consistently across participants and this is often achieved by
535 manualising the intervention (e.g., manual for lifestyle intervention in infertility, see
536 Ockhuijsen et al., 2012). As a self-administered tool the PRCI comes with a two-page leaflet
537 that describes the rationale for the intervention, including the recommendation that it should
538 be read PRCI twice daily. On average women complied with this recommendation (mean
539 number of times read daily 1.97) but a proportion of women used it less frequently. Lower
540 frequency could reflect that women became less interested in using the tool which could
541 impact on PRCI effects.**

542 The PRCI was designed to help women reinterpret the demands of the waiting period in a
543 more positive way and we used the DRK, a measure of treatment specific reactions, to capture
544 the daily effects of PRCI during the waiting period. However, because daily monitoring itself
545 may have an impact on the reporting of emotions (Cohen et al., 1995) we added a monitoring-
546 control group to disentangle between this methodological artefact and genuine effects of
547 PRCI. We considered this control as a strength of the RCT though this may not be the case.
548 In a parallel study, interviews among women with miscarriage showed that the use of the
549 DRK was affecting emotions, as if the DRK itself was an intervention (unpublished data). If
550 daily monitoring is perceived to be an intervention then the lack of difference observed in the
551 present study between the PRCI and the monitoring-control group could have been due to
552 active effects of monitoring or the possibility that active effects attenuated or obscured effects
553 of the PRCI intervention in unknown ways. Further, the PRCI benefits may be due to an
554 interaction between PRCI and monitoring. The use of a monitoring-control could thus be a
555 weakness of the study because assessment and intervention were confounded. A randomised
556 group of women that used only the PRCI without daily monitoring would provide more
557 insight. We collected such data (n=110) and it would seem that daily monitoring attenuates
558 the effects of PRCI on anxiety and the pregnancy rate. However, only a randomised trial
559 could definitely identify the benefits of PRCI when it is administered on its own.

560 Another methodological limitation worth considering is the use of the opt-in method to recruit
561 participants. In this method patients indicate a willingness to be included the study (opt-in)
562 instead of the more conventional approach where all patients are enrolled in the trial unless
563 they have indicated a willingness to be excluded (opt-out). Although the opt-out method
564 produces a larger pool of eligible participants at recruitment, ethical committees often do not
565 approve of this method, as was the case in the present RCT, because it requires repeated
566 contact which may be burdensome for participants (Junghans et al., 2005; Treweek et al.,

567 2010). In an RCT designed to evaluate the effects of the opt-in compared to opt-out
568 recruitment strategies, patients in the opt-in arm were healthier on clinical indicators (e.g.,
569 fewer risk factors, symptoms of disease etc) than patients in the opt-out arm, presumably
570 because they could better manage the demands of the study (Junghans et al., 2005; Treweek et
571 al., 2010). In the present study, it is likely that mainly women who were interested in
572 psychological interventions opted-in to participate. Indeed, the overall percentage of past
573 users (19.7%) of infertility counselling in the present sample was higher than previously
574 reported in a British sample (8.5%) (Boivin et al., 1999). It could be that previous use of more
575 in-depth psychological interventions had an impact on study results. Although numbers were
576 too few in the present study to examine this issue fully it warrants consideration in future
577 trials using the opt-in method. Overall readers should consider these limitations as they may
578 affect generalizability.

579

580 Although PRCI was not associated with benefit on the psychological questionnaires it was on
581 the intervention evaluation form. Positive evaluations on the intervention form could be due
582 to demand characteristics. However, patient and researcher were not connected in any way,
583 and the medical staff did not have access to any study responses, which makes this possibility
584 unlikely. A discrepancy between outcome measures and intervention evaluations has been
585 reported in previous research (Bird et al., 2011; Emery et al., 2003). In a qualitative study, 15
586 trial participants and five staff members were interviewed at the end of a trial evaluating a
587 rehabilitation programme that had previously been highly rated by patients (Bird et al., 2011;
588 Emery et al., 2003). Although no scientific evidence was found for the efficacy of the
589 rehabilitation programme, participants and staff members continued to have strong views
590 about the benefit of the intervention. During the interview one of the staff members suggested
591 that "the trial had killed the intervention". Their perspective was that because the pilot phase

592 had in their opinion been a success, then the process of the RCT must have affected the
593 intervention in such a way as to take away from its benefits. This too may have been an issue
594 for the PRCI trial with, as noted, the addition of monitoring potentially impacting PRCI
595 effects. Bird et al. (2011) recommended that the views and experiences of staff and
596 participants be taken before and after conducting the RCT to evaluate the impact of
597 investigative process on perceptions and we concur with this recommendation. Future
598 research on PRCI could also identify for whom the intervention works best and whether the
599 PRCI could be made more or less effective with change to the item list.

600 The pattern of results, theoretical, empirical and methodological considerations, all point to
601 the main impact of PRCI as being to make the stress of the waiting period more tolerable than
602 in taking away the negative emotions waiting produces. If PRCI was expensive or difficult to
603 administer one might consider the costs and modest (mainly perceived) benefits of PRCI to
604 argue against a recommendation for the waiting period. However, PRCI is self-administered,
605 comprises a sheet of A4, and can be implemented at a time when patients are not in contact
606 with the medical team or other patients for more interpersonal forms of support. As such we
607 contend that the positive emotions and sense of being helped that PRCI generates are
608 sufficient for it to be offered singly or in combination with other interventions to help women
609 manage the demands of the ART waiting period. Future research should investigate whether
610 PRCI helps to make other medical waiting periods more tolerable.

611

612 **Authors roles**

613 H.O. designed the trial, monitored data collection for the whole trial, wrote the statistical
614 analysis plan, cleaned and analysed the data, and drafted and revised the paper. A.H. designed
615 the trial, drafted and revised the paper. M.E. cleaned and analysed the data. N.M. initiated the
616 project, designed the trial and revised the draft paper. J.B. designed the trial, designed

617 intervention and data collection tools, cleaned and analysed the data, and drafted and revised
618 the paper.

619

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625

626 **Conflicts of interest**

627 None declared

628

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