

A randomised controlled trial of a digital intervention (Renewed) to support symptom management, wellbeing and quality of life in cancer survivors

Little, Paul; Bradbury, Katherine; Stuart, Beth; Barnett, Jane; Krusche, Adele; Steele, Mary; Heber, Elena; Easton, Steph; Smith, Kirsten A.; Slodowska-Barabasz, Joanna; Payne, Liz; Corbett, Teresa; Wilde, Laura; Yao, Guiqong Lily; Pollet, Sebastien; Smith, Jazzine; Joseph, Judith; Lawrence, Megan; Böhning, Dankmar; Cheetham-Blake, Tara; Eccles, Diana; Foster, Claire; Geraghty, Adam William Alfred; Leydon, Geraldine; Müller, Andre Matthias; Neal, Richard D.; Osborne, Richard; Rathod, Shanaya; Richardson, Alison; Grimmett, Chloe; Sharman, Geoffrey; Bacon, Roger; Turner, Lesley; Stephens, Richard; Rogers, Kirsty; Raftery, James; Zhu, Shihua; Singh, Karpaul; Webley, Frances; Griffiths, Gareth; Nutall, Jaqui; Chalder, Trudie; Wilkinson, Clare; Watson, Ella; Yardley, Lucy

British Journal of General Practice

DOI:

<https://doi.org/10.3399/BJGP.2023.0262>

E-pub ahead of print: 20/12/2023

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):

Little, P., Bradbury, K., Stuart, B., Barnett, J., Krusche, A., Steele, M., Heber, E., Easton, S., Smith, K. A., Slodowska-Barabasz, J., Payne, L., Corbett, T., Wilde, L., Yao, G. L., Pollet, S., Smith, J., Joseph, J., Lawrence, M., Böhning, D., ... Yardley, L. (2023). A randomised controlled trial of a digital intervention (Renewed) to support symptom management, wellbeing and quality of life in cancer survivors. *British Journal of General Practice*. Advance online publication. <https://doi.org/10.3399/BJGP.2023.0262>

Hawliau Cyffredinol / General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

01. May. 2024

Title. A randomised controlled trial of a digital intervention (Renewed) to support symptom management, wellbeing and quality of life in cancer survivors

Professor Paul Little, BA MBBS MSc MD FRCGP FMedSci orcid 0000-0003-3664-1873³; Dr Katherine Bradbury BSc MSc PhD¹, Professor Beth Stuart PhD orcid: 0000-0001-5432-7437³, Ms Jane Barnett BA Study Manager³, Dr Adele Krusche PhD¹, Dr Mary Steele PhD¹, Dr Elena Heber PhD¹, Ms Steph Easton BSc 0000-0003-3857-8337¹, Dr Kirsten A. Smith PhD³ Joanna Slodowska-Barabasz¹³, Dr Liz Payne PhD¹, Dr Teresa Corbett BA (Hons), MSc, PhD. CPsychol., FHEA orcid: 0000-0002-5620-5377², Dr Laura Wilde PhD, MSc, BSc (Hons), AFHEA, CPsychol orcid 0000-0002-1404-6304¹ Professor Guiqing Lily Yao PhD orcid 0000-0002-0591-9636⁴, Dr Sebastien Pollet PhD orcid 0000-0001-9924-9225¹, Dr Jazzine Smith PhD¹, Dr Judith Joseph PhD¹, Dr Megan Lawrence PhD⁷, Professor Dankmar Böhning PhD⁶ Dr Tara Cheetham-Blake PhD², Professor Diana Eccles MD FRCP orcid 0000-0002-9935-3169⁷, Professor Claire Foster BSc, MSc, PhD, CPsychol 0000-0002-4703-8378⁸, Associate Professor Adam W A Geraghty PhD³, Professor Geraldine Leydon PhD orcid 0000-0001-5986-3300³, Dr Andre Matthias Müller PhD orcid 0000-0001-5770-6723⁹, Professor Richard D Neal MBChB PhD FRCGP orcid 0000-0002-3544-2744¹⁰, Dr Richard Osborne MBBS¹¹, Professor Shanaya Rathod DM MRCPsych orcid 0000-0001-5126-3503¹², Professor Alison Richardson PhD^{2,19}, Dr Chloe Grimmett, PhD, orcid 0000-0002-7540-7206²; Professor Geoffrey Sharman Ph.D, FBCS CITP, 0000-0003-2747-9616⁵, Mr Roger Bacon⁵, Ms Lesley Turner⁵, Mr Richard Stephens MA orcid 0000-0002-0760-2771³, Ms Kirsty Rogers BSc orcid 0000-0001-5394-4003³, Professor James Raftery PhD¹⁷, Dr Shihua Zhu PhD¹⁷, Professor Karpaul Singh PhD¹⁸, Ms Frances Webley MSc⁷, Professor Gareth Griffiths PhD orcid 0000-0002-9579-8021⁷, Ms Jaqui Nutall⁷, Professor Trudie Chalder PhD MSc orcid 0000-0003-0775-1045²⁰, Professor Clare Wilkinson MBBS PhD¹⁵, Professor Eila Watson BSc PhD orcid 0000-0002-3592-1315¹³, Professor Lucy Yardley PhD, 0000-0002-3853-883X^{1 16}.

¹ Department of Psychology, University of Southampton, Southampton, UK,

² School of Health Sciences, University of Southampton, Southampton, UK,

³ Primary Care Research Centre, University of Southampton, Southampton, UK,

⁴ Biostatistics Research Group, University of Leicester, Leicester, UK,

⁵ Patient and Public Involvement team for the CLASP project,

⁶ Mathematical Sciences, University of Southampton, Southampton, UK,

⁷ Southampton Clinical Trials Unit, University of Southampton, Southampton, UK,

Centre for Psychosocial Research in Cancer: CentRIC+, Health Sciences, University of Southampton, UK

⁹ Saw Swee Hock Public School of Health, National University of Singapore, Singapore,

¹⁰ College for Medicine and Health, University of Exeter, Exeter, UK

¹¹ Dorset Cancer Centre, Poole, UK,

¹² Southern Health National Health Service (NHS) Foundation Trust, Southampton, UK,

¹³ Oxford Institute of Nursing, Midwifery and Allied Health Research, Oxford Brookes University, Oxford, UK,

¹⁴ Faculty of Health & Life Sciences, Coventry University, Coventry, UK,

¹⁵ School of Health Sciences, Bangor University, Bangor, UK,

¹⁶ School of Psychological Science, University of Bristol, Bristol, UK

¹⁷ Health Economics Analysis Team, University of Southampton, Southampton, UK

¹⁸ Department of Psychology, University of Calgary, Calgary, Canada,

¹⁹ University Hospital Southampton NHS Foundation Trust

²⁰ Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, Kings College London, London, UK

Correspondence to Professor Little p.little@soton.ac.uk orcid 0000-0003-3664-1873

Tel +44 2380 241050; fax +44 2380 701125

University of Southampton, Aldermoor Health Centre, Aldermoor close, Southampton UK, SO16 5ST

Word count 2573 (2488 originally)

Abstract

Background

Many cancer survivors following primary treatment have prolonged poor quality of life.

Aim. To determine the effectiveness of a bespoke digital intervention to support cancer survivors.

Design. Pragmatic parallel open randomised trial.

Setting. UK general practices.

Methods. People having finished primary treatment (≤ 10 years previously) for colo-rectal, breast or prostate cancers, with European-Organization-for-Research-and-Treatment-of-Cancer QLQ-C30 score <85 , were randomised by online software to: 1) detailed 'generic' digital NHS support ('LiveWell'; $n=906$), 2) a bespoke complex digital intervention ('Renewed'; $n=903$) addressing symptom management, physical activity, diet, weight loss, distress, or 3) 'Renewed-with-support' ($n=903$): 'Renewed' with additional brief email and telephone support.

Results. Mixed linear regression provided estimates of the differences between each intervention group and generic advice: at 6 months (primary time point: n 's respectively 806;749;705) all groups improved, with no significant between-group differences for EORTC QLQ-C30, but global health improved more in both intervention groups. By 12 months there were: small improvements in EORTC QLQ-C30 for Renewed-with-support (versus generic advice: 1.42, 95% CIs 0.33-2.51); both groups improved global health (12 months: renewed: 3.06, 1.39-4.74; renewed-with-support: 2.78, 1.08-4.48), dyspnoea, constipation, and enablement, and lower NHS costs (generic advice £265: in comparison respectively £141 (153-128) and £77 (90-65) lower); and for Renewed-with-support improvement in several other symptom subscales. No harms were identified.

Conclusion. Cancer survivors quality of life improved with detailed generic online support. Robustly developed bespoke digital support provides limited additional short term benefit, but additional longer term improvement in global health enablement and symptom management, with substantially lower NHS costs.

ISRCTN:96374224. Funding:NIHR

Abstract word count 250

Keywords: cancer survivors; global health; resource use

How this fits in

- There are increasing numbers of cancer survivors who have finished their primary treatment whose quality of life remains consistently poor over years.
- There is limited robust evidence for pragmatic, brief interventions to support cancer survivors in primary care - which is where most participants are managed, and where resources are increasingly stretched.
- Cancer survivors quality of life improved with detailed generic online support
- Robustly developed bespoke digital support provided limited additional benefit for cancer survivors in the short term, but modest additional longer term benefit in enabling symptom management and self-rated health, and with significantly reduced costs to the health service.

Introduction.

Although the UK has one of the poorest cancer survival rates among higher income settings¹, the prevalence of cancer survivors has been increasing year on year (<https://www.cancerresearchuk.org>) and by 2040 cancer survivors are likely to represent a quarter of the UK population². The quality of life (QoL) in some cancer survivors is poor, equivalent to chronic diseases^{3 4} and remains persistently poor over years^{5 6}.

Existing interventions to improve QoL are usually delivered by healthcare practitioners⁷. It can be difficult to roll out clinician-based complex behaviour change interventions at scale, because in practice clinicians often lack the time or behavioural counselling skills needed to provide such support⁸. Digital interventions may help⁹, cancer survivors perceive them positively⁹ and some can be effective⁹⁻¹¹ – albeit with limited tailoring, mostly small trials, and few in typical primary care settings. In the UK, there is limited evidence for digital interventions designed for stable cancer survivors to promote cognitive and behavioural changes to improve overall QoL and health. We developed a digital intervention ('Renewed') using the Person-Based-Approach¹², co-producing the intervention with cancer survivors and clinical experts, optimised based on feedback on prototypes¹³.

We report the main results from the Randomised Controlled trial of Renewed. We aimed to assess whether the Renewed intervention, with or without human support, resulted in a difference in Quality of Life and overall wellbeing compared with access to detailed generic advice.

Methods

The protocol for the main trial has been published¹⁴.

Setting and participants

The trial was conducted in NHS General Practices, all but one (in Scotland) were from England and Wales.

Participant inclusion criteria. Contrasting groups of participants (breast cancer survivors (younger and older women); prostate cancer survivors (predominantly older men); and colorectal cancer (a range of ages and gender)) were identified from case record searches; had completed primary treatment (≥ 1 month and ≤ 10 years previously); had internet access; scored ≤ 85 on the EORTC QLQ-30 (the lowest scoring two thirds of the patient group⁶). Participants were mainly recruited by invitation but could be recruited opportunistically.

Participant exclusion criteria: palliative care; active cancer (unless prostate cancer active watchful waiting); another type of cancer in the last five years; current or expected cancer treatment (except hormones); severe mental health problems; breast sarcoma/lymphoma; in the same household as another participant.

Randomisation.

Automated randomisation with a 1:1:1 allocation ratio using Lifeguide software (www.lifeguideonline.org), stratified by:

- cancer type: breast/prostate/colorectal and
- EORTC QLQ-C30 score (64 or less/65 or more – the cut off for the lowest 25% of the distribution ^{6 15}).

Interventions

The development of 'Renewed' has been published¹³. Detail of the content is given in the Supplement. The trial groups were as follows:

- 1) detailed 'generic' digital NHS support ('Live Well';n=906),
- 2) a bespoke complex digital intervention ('Renewed';n=903) addressing symptom management, physical activity, diet, weight loss, distress, or
- 3) 'Renewed-with-support' (n=903): 'Renewed' with additional brief support by email and telephone

Measures and Outcomes

Outcomes were patient self-reported online (baseline, 6 and 12 months unless indicated), and for non-respondents 2 email reminders, two postal administrations (and a £10 voucher at 6 months), and a final telephone follow-up made blind to group. Information from medical records was obtained blind to group.

a. Primary outcome: Quality of Life using the EORTC QLC-30 instrument (version 3) summary score (https://qol.eortc.org/app/uploads/sites/2/2018/02/scoring_of_the_qlq-c30_summary_score.pdf) at 6 and 12 months.

b. Secondary outcomes:

- EORTC QLQ-C30 subscales (baseline, 6 and 12 months): Global self rated Health, Symptom subscales, Functional subscales (e.g. Physical functioning, Social functioning, Emotional wellbeing).
- Depression and Anxiety¹⁶ Fear of Relapse¹⁷ and The Measure Yourself Concerns and Wellbeing questionnaire for Quality of Life¹⁸ (baseline, 12 months)
- Modified enablement scale^{19 20} (12 months)
- Resource use (medication/consultation costs in primary care)
- Other outcomes/measures will be reported in the process analysis (a website satisfaction measure (12 months); PETS for self-reported adherence).
- website usage

Sample size.

We estimated that to detect a difference of 0.3 SMD (standardised mean difference) between intervention and control for each cancer type (80% power; alpha=0.05) required 176 intervention and 176 control participants, 1584 for the three cancers, or 1980 allowing for 20% loss to follow-up. We estimated that the total sample would detect overall differences between intervention groups of 0.15 SMDs which is more realistic for a brief intervention. Cluster effects are possible even in individually randomised designs: assuming 8 participants per intervention group per practice, an ICC of 0.03 (inflation factor $1.21: 1 + (8-1*0.03)$), required 2396 participants. Allowing for some leeway we aimed to recruit 2500 individuals.

Statistical methods.

In accordance with the ISRCTN registration, following a 'feasibility' phase, the initial feasibility study became an internal pilot, providing data for analysis of the whole trial. Data was analysed on an intention to treat basis using Stata version 17 (Statacorp), but the 20 participants were excluded post randomisation largely for reasons of ineligibility (See Fig1). A Statistical analysis plan is available on request. Generalised linear mixed regression models were used for the analysis of continuous variables, controlling for baseline values, stratification variables, covariates (in accordance with ICH-E9 guidance), and a random effect (a random intercept) for practice. The primary analysis used a chained equation multiple imputation model for missing data including all outcomes (including 6 and 12 month time points) as well as all variables included in the analysis model. We used a chained equations approach with a distribution suitable to each variable. This was linear for the EORTC QLQ-C30, HADS, MYCAW, Enablement and BMI. It was logistic for the presence/absence of comorbidities. Guidance suggests that the number of imputations should equal or exceed the percentage of missing data²¹ which would have been 25 in this case, but to minimise the bias in estimating the point estimates, confidence intervals and p-values we chose 100. A complete cases analysis was a sensitivity analysis.

NHS Resource use. Resource use data were collected by a medical record review in primary care – and primary care was our primary focus since that was where we anticipated any differences in resource use might be found. (See appendix for detail).

Role of funder. The funder, NIHR (National Institute for Health and Care Research), had no role in data collection, analysis, interpretation, writing of the manuscript or the decision to submit.

Trial registration and ethics.

The study had ethical approval (NRES Committee NorthWest; Rec Ref 17/NW/0250) and was registered on the ISRCTN data base on 09/08/2017 (ISRCTN 96374224) prior to the recruitment of the first participant.

Results.

Recruitment. 58295 'cold calling' invitations were sent by mail from 494 GP practices. 7883 individuals expressed interest (see appendix for reasons for non participation). 2732 participants were recruited between 12/10/2017 and 2/4/2020 and the most common reason for not wanting to participate was not having current problems (see Supplement Fig1 and Supplement Table 1); 20 patients were excluded post randomisation largely due to being ineligible (e.g. living at the same address).

Engagement.

Patients accessed Renewed a median of 2 times (range 0-268). Most (97%) accessed the Core content of Renewed, with 84% completing the Core content and reaching the 'Homepage' for optional content suitable for their particular context⁹. 45% accessed the optional contents of Renewed. Of those offered facilitator support 31% (235/756) chose to access it.

Baseline characteristics.

These were well balanced between groups (Table 1) and between cancers (Supplement Table 2) except for gender differences between prostate and breast.

Follow-up

By 6 months 83% (2260/2712) and by 12 months 83% (2247/2712) had complete primary outcome data, with slight differences between group: 103/906 for generic advice care (11%), 201/903 (22%) for Renewed with support and 221/903 (24%) for Renewed. Follow up rates for resource use was 87% (2,351/2,712).

EORTC QLQ-30

There was improvement in all groups at 6 months (Supplement fig 2; table 3), with no significant between group differences. However, the Renewed with support group had higher quality of life at 6 months than the generic advice group in the prostate cancer subgroup (2.03, 0.25-3.80). By 12 months there were small improvements in the EORTC QLQ-C30 for Renewed-with-support (1.42, 95% CIs 0.33-2.51). All cancer groups improved but the results were only significant for prostate cancer (Supplement Table 3).

Results for subscales at 6 months

There were significant differences compared with generic advice for self-rated global health in both Renewed groups (Table 4). The Renewed with support group also showed improvement in the physical function and cognitive function subscales.

Results for subscales at 12 months

The generic advice group did not continue to improve, and for both groups at 12 months compared with generic advice most subscales improved, and this was significant for global health (12 months: Renewed: 3.06, 1.39-4.74; Renewed with support: 2.78, 1.08-4.48), dyspnoea, constipation, and enablement (Table 5; Figure 1). The Renewed with support group also showed significant improvement in the physical, emotional, cognitive fatigue and dyspnoea subscales (i.e. 8 subscales in total).

Within group analysis: improvement from baseline (post hoc analysis)

The Minimally clinically important difference (MCID) for the EORTC questionnaire has been determined in unwell cancer patients for major treatments in the active phase of cancer treatment, and has been suggested as between 5 and 10^{22 23} (<https://qol.eortc.org/faq/how-do-i-interpret-qol-scores/how-do-i-interpret-qol-scores/>). More than 40% in each group achieved a 6 point improvement at 6 months with no difference between the groups, and by 12 months continued improvement in both intervention groups (Supplement Table 4), but flattening off for generic advice.

Other secondary outcomes

Since we received only half of other secondary outcome questionnaire data, we have also presented the complete cases data. There was a modest (0.5 point) improvement in anxiety, depression and bothersomeness on the MYCAW1 in the Renewed with support group (Supplement Table 5). Patient Enablement improved in both groups: on average one in three people said they agreed they felt enabled to manage their condition compared to those having generic advice.

Resource use.

Mean primary care NHS costs per participant due to fewer appointments and prescriptions were substantially and significantly lower in Renewed and Renewed with support groups (generic advice £265: and in comparison respectively -£141,-153 to -128; -£77,-90 to -65; see Supplement Table 6) .

Results for cancer subgroups

There were no significant interaction terms and the subgroup results were generally in line with the main trial results (Supplement Table 7). After controlling for cancer type, males did significantly better than females on the primary outcome at 6 months. There was also a suggestion that there could be more benefit among longer term survivors.

Harms. There were no reports of harms in any group. There were 6 deaths: 1 in the generic advice group, 3 in Renewed with support and 2 in Renewed.

Table 1. Baseline characteristics by intervention group

	Generic advice (n=906)	Renewed with support (n=903)	Renewed (n=903)	Total (n=2712)
Age (years)				
Mean (s.d)	64.5 (10.9)	64.5 (11.2)	64.5 (10.7)	64.5 (10.9)
*Baseline EORTC QLQ-C30 score				
Mean (s.d)	72.1 (12.2)	72.5 (11.8)	72.7 (11.7)	72.4 (11.9)
Education status				
School leaver	397/906 (43.8%)	412/903 (45.6%)	377/903 (41.8%)	1186/2712 (43.7%)
College	231/906 (25.5%)	237/903 (26.3%)	241/903 (26.7%)	709/2712 (26.1%)
Degree or higher	278/906 (30.7%)	254/903 (28.1%)	285/903 (31.6%)	817/2712 (30.1%)
Marital Status				
Single	64/906 (7.1%)	46/902 (5.1%)	53/902 (5.9%)	163/2710 (6.0%)
Living with partner	52/906 (5.7%)	73/902 (8.1%)	63/902 (7.0%)	188/2710 (6.9%)
Married	646/906 (71.3%)	624/902 (69.2%)	639/902 (70.8%)	1909/2710 (70.4%)
Divorced	65/906 (7.2%)	82/902 (9.1%)	76/902 (8.4%)	223/2710 (8.2%)
Widowed	58/906 (6.4%)	61/902 (6.8%)	59/902 (6.5%)	178/2710 (6.6%)
Separated	21/906 (2.3%)	16/902 (1.8%)	12/902 (1.3%)	49/2710 (1.8%)
Ethnicity				
Non-White	22/906 (2.4%)	19/902 (2.1%)	20/902 (2.2%)	61/2710 (2.3%)
White	884/906 (97.6%)	883/902 (97.9%)	882/902 (97.8%)	2649/2710 (97.8%)
BMI				
Mean (s.d)	28.0 (5.5)	28.2 (5.5)	28.0 (5.4)	28.1 (5.5)
Cancer group				
Bowel/Colorectal	143/906 (15.8%)	143/903 (15.8%)	146/903 (16.2%)	432/2712 (15.9%)
Breast	474/906 (52.3%)	471/903 (52.3%)	471/903 (52.2%)	1416/2712 (52.2%)
Prostate	289/906 (31.9%)	289/903 (32.0%)	286/903 (31.7%)	864/2712 (31.9%)
Comorbidities				
Cardio	291/779 (37.4%)	325/787 (41.3%)	329/789 (41.7%)	945/2355 (40.1%)
Lung	130/779 (16.7%)	126/787 (16.0%)	149/789 (18.8%)	405/2355 (17.2%)
Other	548/779 (70.4%)	545/787 (69.3%)	563/789 (71.4%)	1656/2355 (70.3%)
Gender				
Male	379/906 (41.8%)	380/903 (42.1%)	368/903 (40.8%)	1127/2712 (41.6%)
Female	527/906 (58.2%)	523/903 (57.9%)	535/903 (59.3%)	1585/2712 (58.4%)
Time since last cancer treatment (years)				
Mean (s.d)	4.0 (3.0)	4.1 (3.2)	3.9 (3.3)	4.0 (3.1)

*range 0-100, higher scores reflect higher quality of life

Table 2 Baseline EORTC QLQ-C30 Subscale by intervention group

	Generic advice (n=906)	Renewed with support (n=903)	Renewed (n=903)	Total (n=2712)
Global health				
Mean (s.d)	60.4 (17.3)	60.7 (17.0)	59.9 (16.2)	60.3 (16.8)
Functional subscales				
Physical function				
Mean (s.d)	76.9 (19.0)	75.7 (19.4)	76.9 (17.8)	76.5 (18.7)
Role function				
Mean (s.d)	66.9 (26.6)	68.0 (26.1)	67.6 (25.6)	67.5 (26.1)
Emotional function				
Mean (s.d)	64.4 (22.6)	64.2 (23.2)	65.2 (22.6)	64.6 (22.8)
Cognitive function				
Mean (s.d)	69.9 (22.1)	71.2 (21.4)	72.4 (20.8)	71.2 (21.4)
Social function				
Mean (s.d)	66.1 (26.0)	67.1 (26.6)	66.9 (25.7)	66.7 (26.1)
Symptom subscales				
Fatigue				
Mean (s.d)	44.7 (20.3)	44.2 (20.6)	44.3 (19.4)	44.4 (20.1)
Nausea and vomiting				
Mean (s.d)	6.9 (13.2)	6.8 (12.7)	7.0 (12.6)	6.9 (12.8)
Pain				
Mean (s.d)	33.4 (27.1)	32.8 (26.8)	32.6 (27.6)	32.9 (27.1)
Dyspnoea				
Mean (s.d)	24.1 (26.5)	23.2 (25.9)	24.2 (26.5)	23.8 (26.3)
Insomnia				
Mean (s.d)	50.8 (31.9)	50.6 (31.3)	50.4 (30.3)	50.6 (31.2)
Appetite loss				
Mean (s.d)	14.0 (22.3)	13.4 (21.2)	12.8 (21.3)	13.4 (21.6)
Constipation				
Mean (s.d)	19.9 (26.5)	20.0 (26.3)	18.6 (27.2)	19.5 (26.7)
Diarrhoea				
Mean (s.d)	13.7 (22.4)	13.0 (22.4)	14.5 (23.8)	13.8 (22.9)
Financial difficulties				
Mean (s.d)	11.6 (24.3)	12.8 (24.4)	11.8 (24.3)	12.1 (24.3)

Table 3. EORTC QLQ-30 at 6 and 12 months. Means for each group, and adjusted differences between Renewed groups and Generic advice.

	All participants		
6 months	Generic advice	Renewed with support	Renewed
- Mean (s.d.)*	76.0 (14.31)	76.7 (14.41)	76.1 (13.99)
- Number of Complete cases	806	705	749
Difference in means:			
- Complete cases	REF	0.50 (-0.67, 1.66)	-0.42 (-1.57, 0.72)
- Imputed (100 imputations)	REF	0.52 (-0.53, 1.57)	-0.20 (-1.23, 0.84)
12 months			
- Mean (s.d.)	75.7 (15.13)	77.2 (14.07)	77.0 (14.42)
- Number of Complete cases	803	702	742
Difference in means:			
- Complete cases	REF	1.11 (-0.10, 2.31)	0.72 (-0.46, 1.91)
- Imputed (100 imputations)	REF	1.42 (0.33, 2.51)	0.94 (-0.13, 2.01)

Figure 1. Graphical representation of improvement of global health score over time

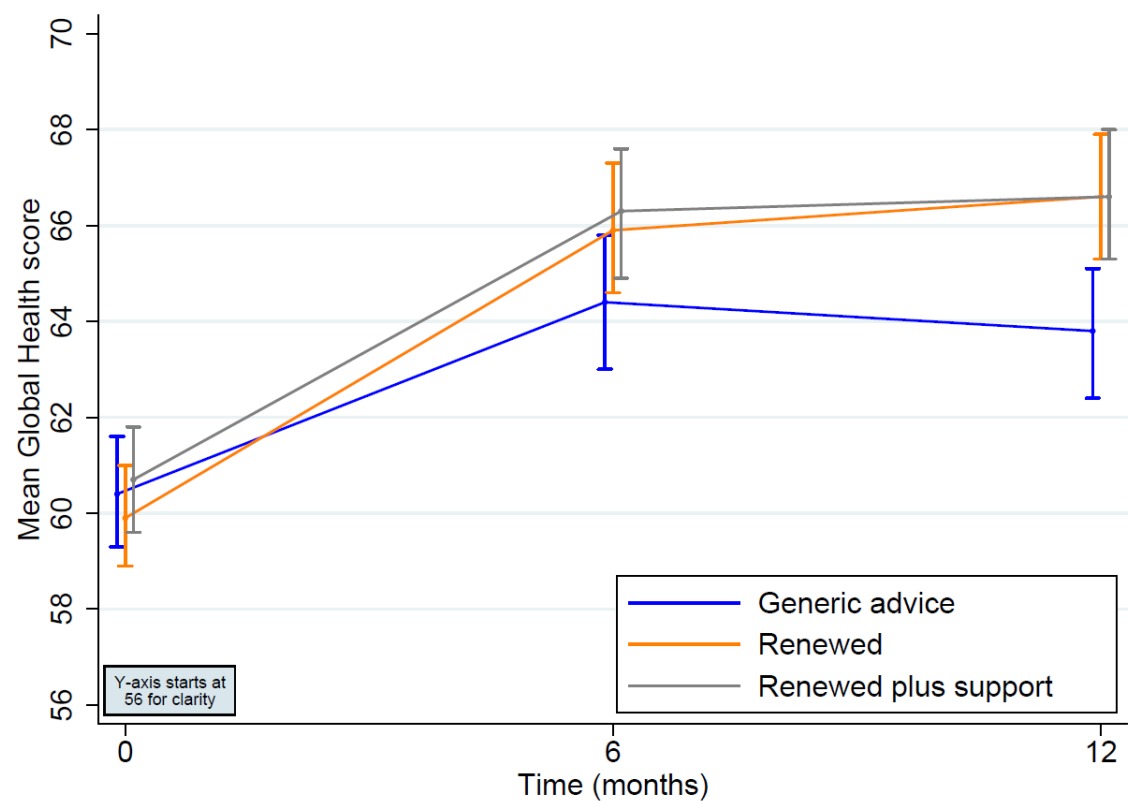


Table 4. Results for EORTC QLC-30 subscales at 6 months. Means for each group, and adjusted differences between Renewed groups and Generic advice.

	Generic advice	Renewed with Support		Renewed	
	Mean (s.d.)	Mean (s.d.)	Imputed (100 imputations)	Mean (s.d.)	Imputed (100 imputations)
*Global health	64.4 (19.89)	66.3 (18.54)	1.82 (0.14, 3.52)	65.9 (19.11)	1.88 (0.18, 3.58)
*Functional subscales					
Physical function	77.7 (20.68)	78.7 (19.88)	2.00 (0.64, 3.36)	78.2 (19.88)	0.50 (-0.82, 1.82)
Role function	71.9 (28.36)	71.3 (28.14)	-1.01 (-3.45, 1.42)	71.0 (27.49)	-1.06 (-3.44, 1.31)
Emotional function	69.8 (22.72)	70.5 (22.15)	0.79 (-1.01, 2.60)	70.0 (21.93)	-0.05 (-1.87, 1.76)
Cognitive function	73.5 (22.10)	76.5 (20.86)	2.32 (0.52, 4.12)	75.5 (21.33)	0.69 (-1.10, 2.48)
Social function	71.8 (27.55)	73.6 (27.46)	1.46 (-0.83, 3.75)	72.7 (26.68)	0.70 (-1.58, 2.97)
¹Symptom subscales					
Fatigue	38.6 (22.60)	37.2 (22.75)	-1.18 (-3.08, 0.73)	38.7 (22.51)	0.20 (-1.72, 2.12)
Nausea and vomiting	5.5 (11.62)	6.0 (12.67)	0.55 (-0.59, 1.70)	5.8 (11.78)	0.26 (-0.85, 1.36)
Pain	31.5 (28.07)	31.8 (28.19)	0.43 (-1.89, 2.75)	32.2 (28.33)	0.81 (-1.49, 3.12)
Dyspnoea	20.8 (25.81)	19.0 (24.65)	-1.47 (-3.64, 0.70)	20.11 (26.41)	-0.92 (-3.00, 1.17)
Insomnia	41.5 (31.22)	41.5 (32.43)	0.001 (-2.81, 2.81)	42.0 (31.15)	0.39 (-2.38, 3.16)
Appetite loss	11.4 (21.37)	10.8 (20.83)	-0.36 (-2.28, 1.56)	11.1 (20.65)	0.07 (-1.81, 1.95)
Constipation	17.0 (25.79)	15.6 (24.86)	-1.51 (-3.75, 0.73)	15.8 (25.50)	-0.68 (-2.88, 1.52)
Diarrhoea	11.0 (20.62)	11.2 (22.66)	0.55 (-1.49, 2.58)	12.2 (23.06)	0.89 (-1.15, 2.92)
Financial difficulties	10.4 (23.42)	11.8 (23.82)	1.03 (-0.83, 2.89)	11.44 (23.02)	1.02 (-0.85, 2.89)

*range 0-100, higher scores reflect improved health or functioning; ¹range 0-100, lower scores reflect improved symptom control

Table 5. Results for EORTC QLQ-30 subscales at 12 months. Means for each group, and adjusted differences between Renewed groups and Generic advice.

	Generic advice	Renewed with Support		Renewed group	
	Mean (s.d.)	Mean (s.d.)	Imputed (100 imputations)	Mean (s.d.)	Imputed (100 imputations)
Global health	63.8 (20.46)	66.6 (19.01)	2.78 (1.08, 4.48)	66.6 (18.68)	3.06 (1.39, 4.74)
Functional subscales					
Physical function	78.3 (21.12)	79.6 (19.57)	2.25 (0.88, 3.62)	78.5 (20.54)	0.14 (-1.22, 1.50)
Role function	71.8 (28.63)	72.5 (27.57)	0.02 (-2.36, 2.41)	73.2 (27.63)	0.89 (-1.50, 3.27)
Emotional function	68.9 (23.13)	71.5 (22.35)	2.72 (0.84, 4.61)	70.2 (22.82)	0.99 (-0.87, 2.84)
Cognitive function	73.6 (22.43)	76.3 (20.59)	1.92 (0.13, 3.71)	76.0 (21.33)	1.12 (-0.65, 2.89)
Social function	72.9 (28.45)	75.6 (27.62)	2.22 (-0.20, 4.64)	74.7 (27.83)	1.31 (-1.10, 3.72)
Symptom subscales					
Fatigue	38.4 (22.91)	35.6 (22.50)	-2.67 (-4.58, -0.75)	37.0 (22.78)	-1.25 (-3.15, 0.66)
Nausea and vomiting	6.1 (12.58)	5.9 (12.58)	-0.24 (-1.41, 0.93)	5.2 (12.02)	-0.96 (-2.11, 0.20)
Pain	31.2 (28.32)	30.9 (27.08)	-0.22 (-2.53, 2.10)	31.8 (28.79)	0.86 (-1.48, 3.20)
Dyspnoea	22.2 (19.26)	19.3 (25.45)	-2.73 (-4.92, -0.55)	19.7 (25.31)	-2.78 (-4.91, -0.64)
Insomnia	42.5 (32.56)	41.2 (32.55)	-1.30 (-4.14, 1.55)	40.1 (30.84)	-2.27 (-5.08, 0.54)
Appetite loss	11.0 (20.46)	10.3 (20.15)	-0.68 (-2.53, 1.18)	10.5 (20.88)	-0.13 (-1.96, 1.69)
Constipation	18.9 (26.29)	16.6 (25.22)	-2.36 (-4.62, -0.11)	15.5 (24.95)	-2.77 (-4.99, -0.55)
Diarrhoea	11.8 (21.31)	11.2 (21.60)	-0.57 (-2.51, 1.37)	11.9 (21.40)	-0.42 (-2.38, 1.53)
Financial difficulties	9.2 (21.60)	9.8 (21.49)	0.28 (-1.49, 2.04)	9.5 (21.61)	0.36 (-1.40, 2.13)

Discussion.

Summary.

This is one of the few trials of brief multidimensional support for cancer and documents improvement in quality of life among participants given detailed evidence-based generic lifestyle support – something which does not happen currently in everyday practice. In the shorter term (6 months) compared with generic advice there no evidence of between group differences in overall quality of life, but global health improved in both groups. There was a small significant difference for Renewed with support by 12 months for quality of life. Modest longer-term differences for both the Renewed groups compared with generic advice were found in global rating of health, symptom management, and enablement by 12 months, with a substantial reduction in NHS primary care costs in both groups.

Strengths and Weaknesses

The complex intervention was developed robustly with a user centred approach, the Person-Based-Approach²⁴⁻²⁶, and is one of the largest trials to assess the impact of brief support. ‘Cold calling’ invitations provide lowish uptake rates, raising concerns about generaliseability. However, in the PRIMIT trial which used similar recruitment methods²⁵ behavioural intentions were in fact *lower* than was subsequently found when people used the intervention outside the trial context²⁷ - which suggests we may have under-estimated the effectiveness of Renewed. Reassuringly only 25% (2649/10697) declined due to lack of internet access, and the sample were similar to observational studies of cancer survivors^{9 28 29}, which suggests generaliseable results. The choice of overall EORTC QLQ-30 score, albeit the most widely used outcome, is probably a blunt instrument for low intensity interventions (with 4 point responses for all items except global health), and other instruments might have been more suitable in retrospect - but had the disadvantage of many more items³⁰. The ‘generic’ NHS website has lots of click-throughs to more in depth advice and support, and there was regular follow-up by the research team which may explain the useful improvement seen in the control group. The limited number of times participants engaged is probably not a major issue: we have found previously with digital interventions that many people can get substantial benefit from brief engagement with core content provided it can deliver the essential advice^{26 31} and Renewed was designed with this objective – hence the importance of 97% of participants having used the core session.

Comparison with other studies

The improvement in all groups is unlikely to reflect the natural history or regression to the mean since groups with poor quality of life remain stable and consistently poor after 2 years⁵. The primary analysis time point was chosen as 6 months because that was the timescale previous systematic reviews had reported³². The small significant difference for Renewed with support by 12 months for quality of life was particularly important for the subgroup with prostate cancer, helping address the need for support in this patient group^{33 34}. Compared with generic advice at 12 months for both groups there was significantly improved global health, dyspnoea, constipation, and enablement, and substantially lower

NHS costs and for Renewed-with-support significant differences for four other symptom subscales. This pattern makes chance a very unlikely explanation of the findings. Most important of the subscales is arguably the improvement in self rated global health, since it has consistently been shown to be a strong predictor of mental health, physical health and mortality in the longer term³⁵⁻⁴¹. Global health improved significantly more in both renewed groups compared to the generic group at both 6 and 12 months, equivalent to approximately 40% of the sample rating their global health one point higher on a 13 point scale compared with generic advice. The finding that enablement improved with Renewed (both with and without support), albeit with less complete data, is probably also important in its own right since in the CREW colorectal cohort confidence to self-manage was highly predictive of subsequent health and wellbeing outcomes⁶.

There is some evidence from systematic reviews of trials that yoga, physical exercise more generally, cognitive behavioural therapy (CBT), mindfulness-based stress reduction (MBSR) programmes, and dietary interventions can improve quality of life^{7 32 42-47} but very little evidence of benefit at 6 months from brief multi-dimensional home based interventions⁴⁷ and no evidence of benefit in the longer term. Cancer survivors are positive about digital interventions⁹ and some can be effective⁹⁻¹¹ – albeit not sufficiently tailored, and most trials being small and few in typical primary care settings. To our knowledge there has been no trial with longer term follow-up of robustly developed, brief multidimensional support for cancer survivors in primary care for pragmatic applicability in everyday practice.

Implications for practice and future research.

Currently many cancer survivors have consistently poor quality of life , but there is limited support in primary care where most participants are managed, and where resources are increasingly stretched. Cancer survivors improved with detailed online generic support, but there were further small improvements over the longer term with the bespoke RENEWED intervention. The important reduction in NHS costs in primary care and benefits for symptom management and self rated global health achieved with very brief, scalable, intervention suggests a more widespread implementation study of the RENEWED intervention is warranted.

Acknowledgements.

Contributors: All authors contributed significantly to the development of the protocol. All authors contributed to overseeing the management of the study, agreeing the analysis plan, and to the write-up of the paper. PL with LY had the initial ideas, and jointly led the grant application. LY and KB led the development of the intervention with support from MS TC AWG AK EH SE TC-B JS-B AM KS LW LP KS RB TB KS LT AR EW KF PL. JB, KM, ML K R_R performed day to day management of the study supervised by PL, LY and KB and supported by all authors at study management meetings. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. BS performed the analysis with input from PL, but all authors contributed to data interpretation. PL did the initial drafting of the paper and is the guarantor, but all authors contributed to the redrafting of the paper.

Funding. This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research programme (grant ref No RP-PG-0514-20001). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. LY is an NIHR Senior Investigator and her research programme is partly supported by NIHR Applied Research Collaboration (ARC)-West and NIHR Health Protection Research Unit (HPRU) for Behavioural Science and Evaluation. The Renewed intervention was developed using LifeGuide software, which is partly supported by the NIHR Southampton Biomedical Research Centre (BRC).

Competing interests. There was no support from any organisation other than the NIHR for the submitted work and no financial relationships with organisations that might have an interest in the work.

Data sharing statement. Consent was not obtained from participants for data sharing but requests for anonymised data release can be made to PL or LY with a rationale for further analyses.

Proposed dissemination plans

We will disseminate the results via conferences, social media (twitter handles), but also via our PPI collaborators and their networks. Working with national policy leads for personalised care and improving quality of life we propose developing resources to introduce Renewed as part of the national Cancer Alliance learning and development programme and equivalent leads/networks in devolved nations.

We will brief policy leads responsible for digital to support personalised care (part of the NHSE personalised care programme). Similarly we will brief the voluntary and charity sector who offer information and support services e.g Macmillan cancer support, bowel cancer UK, breast cancer now and Cancer Research UK. We also propose working with Macmillan Cancer Support to reach GPs and primary care networks including e-newsletter aimed at GPs, primary care cancer leads and wider primary care community

References

1. Coleman M, Forman D, Bryant H, et al. Cancer survival in Australia, Canada, Denmark, Norway, Sweden, and the UK, 1995-2007 (the International Cancer Benchmarking Partnership): an analysis of population-based cancer registry data. *Lancet* 2010;DOI:10.1016/S0140-6736(10)62231-3
2. Maddams J, Utley M, Møller H. Projections of cancer prevalence in the United Kingdom, 2010-2040. *Br J Cancer* 2012;107(7):1195-202. doi: 10.1038/bjc.2012.366 [published Online First: 2012/08/16]
3. Elliott J, Fallows A, Staesky L, et al. The health and well-being of cancer survivors in the UK: findings from a population-based survey. *British Journal of Cancer* 2011;105:S11 doi:10.1038/bjc.2011.418 www.bjcancer.com-S20.
4. Richards M. Quality of life of cancer survivors in England: Report on a pilotsurvey using Patient Reported Outcome Measures (PROMS). London: DOH (on line): <https://www.wp.dh.gov.uk/publications> 2012.
5. Wheelwright S, Permyakova NV, Calman L, et al. Does quality of life return to pre-treatment levels five years after curative intent surgery for colorectal cancer? Evidence from the ColoRECTal Wellbeing (CREW) study. *PLoS One* 2020;15(4):e0231332. doi: 10.1371/journal.pone.0231332 [published Online First: 2020/04/10]
6. Foster C, Haviland J, Winter J, et al. Pre-Surgery Depression and Confidence to Manage Problems Predict Recovery Trajectories of Health and Wellbeing in the First Two Years following Colorectal Cancer: Results from the CREW Cohort Study. *PLoS One* 2016;11(5):e0155434. doi: 10.1371/journal.pone.0155434 [published Online First: 2016/05/14]
7. Duncan M, Moschopoulou E, Herrington E, et al. Review of systematic reviews of non-pharmacological interventions to improve quality of life in cancer survivors. *BMJ Open* 2017;7(11):e015860. doi: 10.1136/bmjopen-2017-015860 [published Online First: 2017/12/01]
8. Ware LJ, Williams S, Bradbury K, et al. Exploring weight loss services in primary care and staff views on using a web-based programme. *Inform Prim Care* 2012;20(4):283-8. doi: 10.14236/jhi.v20i4.18 [published Online First: 2012/01/01]
9. Corbett T, Singh K, Payne L, et al. Understanding acceptability of and engagement with Web-based interventions aiming to improve quality of life in cancer survivors: A synthesis of current research. *Psychooncology* 2018;27(1):22-33. doi: 10.1002/pon.4566 [published Online First: 2017/10/19]
10. Leslie M, Beatty L, Hulbert-Williams L, et al. Web-Based Psychological Interventions for People Living With and Beyond Cancer: Meta-Review of What Works and What Does Not for Maximizing Recruitment, Engagement, and Efficacy. *JMIR Cancer* 2022;8(3):e36255. doi: 10.2196/36255 [published Online First: 2022/07/09]
11. Agboola SO, Ju W, Elfiky A, et al. The effect of technology-based interventions on pain, depression, and quality of life in patients with cancer: a systematic review of randomized controlled trials. *J Med Internet Res* 2015;17(3):e65. doi: 10.2196/jmir.4009 [published Online First: 2015/03/21]
12. Yardley L, Morrison L, Bradbury K, et al. The Person-Based Approach to Intervention Development: Application to Digital Health-Related Behavior Change Interventions. *J Med Internet Res* 2015;17(1):e30.
13. Bradbury K, Steele M, Corbett T, et al. Developing a digital intervention for cancer survivors: an evidence-, theory- and person-based approach. *NPJ Digit Med* 2019;2:85. doi: 10.1038/s41746-019-0163-4 [published Online First: 2019/09/12]
14. Krusche A, Bradbury K, Corbett T, et al. Renewed: Protocol for a randomised controlled trial of a digital intervention to support quality of life in cancer survivors. *BMJ Open* 2019;9(3):e024862. doi: 10.1136/bmjopen-2018-024862 [published Online First: 2019/03/04]
15. Foster C, Grimmett C, May CM, et al. A web-based intervention (RESTORE) to support self-management of cancer-related fatigue following primary cancer treatment: a multi-centre proof of concept randomised controlled trial. *Support Care Cancer* 2016;24(6):2445-53. doi: 10.1007/s00520-015-3044-7 [published Online First: 2015/12/07]
16. Zigmond A, Snaith R. The Hospital Anxiety and Depression rating scale. *Acta Psychiatrica Scandinavica* 1983;67:361-70.
17. Greenberg DB, Kornblith AB, Herndon JE, et al. Quality of life for adult leukemia survivors treated on clinical trials of Cancer and Leukemia Group B during the period 1971-1988: predictors for later psychologic distress. *Cancer* 1997;80(10):1936-44. doi: 10.1002/(sici)1097-0142(19971115)80:10<1936::aid-cnrcr10>3.0.co;2-z [published Online First: 1997/11/20]

18. Paterson C, Thomas K, Manasse A, et al. Measure Yourself Concerns and Wellbeing (MYCaW): an individualised questionnaire for evaluating outcome in cancer support care that includes complementary therapies. *Complement Ther Med* 2007;15(1):38-45. doi: 10.1016/j.ctim.2006.03.006 [published Online First: 2007/03/14]
19. Howie J, Heaney D, Maxwell M, et al. Quality at general practice consultations: cross sectional survey. *BMJ* 1999;319:738-43.
20. Little P, Lewith G, Webley F, et al. Randomised controlled trial of Alexander technique lessons, exercise, and massage (ATEAM) for chronic and recurrent back pain. *BMJ* 2008;337: doi: 10.1136/bmj.a884.
21. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30(4):377-99. doi: 10.1002/sim.4067 [published Online First: 2011/01/13]
22. Kawahara T, Taira N, Shiroya T, et al. Minimal important differences of EORTC QLQ-C30 for metastatic breast cancer patients: Results from a randomized clinical trial. *Qual Life Res* 2022;31(6):1829-36. doi: 10.1007/s11136-021-03074-y [published Online First: 2022/01/05]
23. Musoro JZ, Coens C, Greimel E, et al. Minimally important differences for interpreting European Organisation for Research and Treatment of Cancer (EORTC) Quality of life Questionnaire core 30 scores in patients with ovarian cancer. *Gynecol Oncol* 2020;159(2):515-21. doi: 10.1016/j.ygyno.2020.09.007 [published Online First: 2020/09/26]
24. Yardley L, Ainsworth B, Arden-Close E, et al. The person-based approach to enhancing the acceptability and feasibility of interventions. *Pilot and feasibility studies* 2015;1:37. doi: 10.1186/s40814-015-0033-z [published Online First: 2015/10/26]
25. Little P, Stuart B, Hobbs FDR. An internet-delivered handwashing intervention to modify influenza-like illness and respiratory infection transmission (PRIMIT): a primary care randomised trial. *Lancet* 2015;DOI: [http://dx.doi.org/10.1016/S0140-6736\(15\)60127-1](http://dx.doi.org/10.1016/S0140-6736(15)60127-1)
26. Little P, Stuart B, Hobbs FR, et al. An internet-based intervention with brief nurse support to manage obesity in primary care (POWeR+): a pragmatic, parallel-group, randomised controlled trial. *The lancet Diabetes & endocrinology* 2016 doi: 10.1016/s2213-8587(16)30099-7 [published Online First: 2016/07/31]
27. Ainsworth B, Miller S, Denison-Day J, et al. Infection Control Behavior at Home During the COVID-19 Pandemic: Observational Study of a Web-Based Behavioral Intervention (Germ Defence). *J Med Internet Res* 2021;23(2):e22197. doi: 10.2196/22197 [published Online First: 2021/02/11]
28. Blane DN, Lewandowska M. Living with cancer and multimorbidity: the role of primary care. *Curr Opin Support Palliat Care* 2019;13(3):213-19. doi: 10.1097/spc.0000000000000454 [published Online First: 2019/07/28]
29. Keats MR, Cui Y, DeClercq V, et al. Burden of multimorbidity and polypharmacy among cancer survivors: a population-based nested case-control study. *Support Care Cancer* 2021;29(2):713-23. doi: 10.1007/s00520-020-05529-3 [published Online First: 2020/05/24]
30. Avis NE, Ip E, Foley KL. Evaluation of the Quality of Life in Adult Cancer Survivors (QLACS) scale for long-term cancer survivors in a sample of breast cancer survivors. *Health Qual Life Outcomes* 2006;4:92. doi: 10.1186/1477-7525-4-92 [published Online First: 2006/12/05]
31. Ainsworth B, Steele M, Stuart B, et al. Using an Analysis of Behavior Change to Inform Effective Digital Intervention Design: How Did the PRIMIT Website Change Hand Hygiene Behavior Across 8993 Users? *Annals of behavioral medicine : a publication of the Society of Behavioral Medicine* 2017;51(3):423-31. doi: 10.1007/s12160-016-9866-9 [published Online First: 2016/12/03]
32. Mishra S, Scherer R, Geigle P, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst Rev* 2012;Issue 8.:Art. No.: CD007566. DOI:10.1002/14651858.CD007566.pub2.
33. Larkin D, Birtle AJ, Bradley L, et al. A systematic review of disease related stigmatization in patients living with prostate cancer. *PLoS One* 2022;17(2):e0261557. doi: 10.1371/journal.pone.0261557 [published Online First: 2022/02/12]
34. Prashar J, Schartau P, Murray E. Supportive care needs of men with prostate cancer: A systematic review update. *Eur J Cancer Care (Engl)* 2022:e13541. doi: 10.1111/ecc.13541 [published Online First: 2022/01/18]
35. Idler EL, Benyamini Y. Self-rated health and mortality: a review of twenty-seven community studies. *J Health Soc Behav* 1997;38(1):21-37. [published Online First: 1997/03/01]
36. Ambresin G, Chondros P, Dowrick C, et al. Self-rated health and long-term prognosis of depression. *Annals of family medicine* 2014;12(1):57-65. doi: 10.1370/afm.1562

37. Berchick ER, Lynch SM. Regional Variation in the Predictive Validity of Self-Rated Health for Mortality. *SSM Popul Health* 2017;3:275-82. doi: 10.1016/j.ssmph.2017.01.010 [published Online First: 2017/01/31]
38. DeSalvo KB, Bloser N, Reynolds K, et al. Mortality prediction with a single general self-rated health question. A meta-analysis. *Journal of general internal medicine* 2006;21(3):267-75. doi: 10.1111/j.1525-1497.2005.00291.x [published Online First: 2005/12/07]
39. Dowd JB, Zajacova A. Does the predictive power of self-rated health for subsequent mortality risk vary by socioeconomic status in the US? *International journal of epidemiology* 2007;36(6):1214-21. doi: 10.1093/ije/dym214 [published Online First: 2007/11/01]
40. Janszky I, Lekander M, Blom M, et al. Self-rated health and vital exhaustion, but not depression, is related to inflammation in women with coronary heart disease. *Brain, behavior, and immunity* 2005;19(6):555-63. doi: 10.1016/j.bbi.2005.01.001 [published Online First: 2005/10/11]
41. Jylhä M. What is self-rated health and why does it predict mortality? Towards a unified conceptual model. *Soc Sci Med* 2009;69(3):307-16. doi: 10.1016/j.socscimed.2009.05.013 [published Online First: 2009/06/13]
42. Kassianos AP, Raats MM, Gage H, et al. Quality of life and dietary changes among cancer patients: a systematic review. *Qual Life Res* 2015;24(3):705-19. doi: 10.1007/s11136-014-0802-9 [published Online First: 2014/09/15]
43. McGettigan M, Cardwell CR, Cantwell MM, et al. Physical activity interventions for disease-related physical and mental health during and following treatment in people with non-advanced colorectal cancer. *Cochrane Database Syst Rev* 2020;5(5):Cd012864. doi: 10.1002/14651858.CD012864.pub2 [published Online First: 2020/05/04]
44. Schell LK, Monsef I, Wöckel A, et al. Mindfulness-based stress reduction for women diagnosed with breast cancer. *Cochrane Database Syst Rev* 2019;3(3):Cd011518. doi: 10.1002/14651858.CD011518.pub2 [published Online First: 2019/03/28]
45. Cramer H, Lauche R, Klose P, et al. Yoga for improving health-related quality of life, mental health and cancer-related symptoms in women diagnosed with breast cancer. *Cochrane Database Syst Rev* 2017;1(1):Cd010802. doi: 10.1002/14651858.CD010802.pub2 [published Online First: 2017/01/04]
46. Bennett S, Pigott A, Beller EM, et al. Educational interventions for the management of cancer-related fatigue in adults. *Cochrane Database Syst Rev* 2016;11(11):Cd008144. doi: 10.1002/14651858.CD008144.pub2 [published Online First: 2016/11/25]
47. Cheng KKF, Lim YTE, Koh ZM, et al. Home-based multidimensional survivorship programmes for breast cancer survivors. *Cochrane Database Syst Rev* 2017;8(8):Cd011152. doi: 10.1002/14651858.CD011152.pub2 [published Online First: 2017/08/25]
48. Bradbury K, Morton K, Band R, et al. Understanding how primary care practitioners perceive an online intervention for the management of hypertension. *BMC Med Inform Decis Mak* 2017;17(1):5. doi: 10.1186/s12911-016-0397-x [published Online First: 2017/01/11]
49. Cuijpers P, Van Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. *Clin Psych Rev* 2007;27:318-26.
50. Thorn J, Man MS, Chaplin K, et al. Cost-effectiveness of a patient-centred approach to managing multimorbidity in primary care: a pragmatic cluster randomised controlled trial. *BMJ Open* 2020;10(1):e030110. doi: 10.1136/bmjopen-2019-030110 [published Online First: 2020/01/22]

