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

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

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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 settings[1], 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 population[2]. 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 practitioners [7]. 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 support[8]. Digital interventions may help[9], cancer survivors perceive them positively[9] and some can be effective[9-11] – 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-Approach[12], co-producing the intervention with cancer survivors and clinical experts, optimised based on feedback on prototypes[13].

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 published[14].

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 group[6]). 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 published[13]. 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 Anxiety[16] Fear of Relapse [17] and The Measure Yourself Concerns and Wellbeing questionnaire for Quality of Life [18] (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 data[21] 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 context[9]. 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 (Supplment 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**

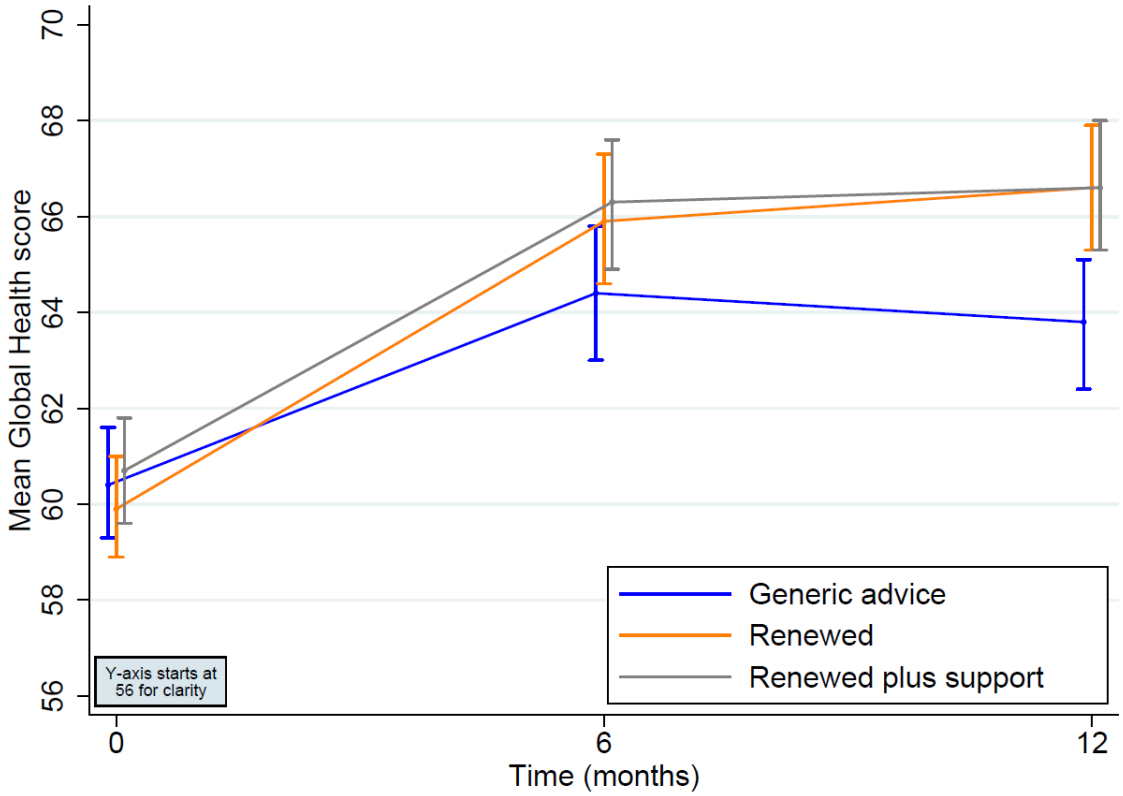

Table 4. Results for EORTC QLC-30 subscales at 6 months. Means for each group, and adjusted differences between Renewed groups and Generic advice.

	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)
[1]**Symptom 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; [1]range 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-Approach [24-26], 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 methods[25] behavioural intentions were in fact *lower* than was subsequently found when people used the intervention outside the trial context[27] - 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 items [30]. 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 wit 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 years[5]. The primary analysis time point was chosen as 6 months because that was the timescale previous systematic reviews had reported[32]. 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 term[35-41]. 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 outcomes[6].

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 interventions[47] and no evidence of benefit in the longer term. Cancer survivors are positive about digital interventions[9] and some can be effective[9-11] – 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.

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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

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