

## **Survivorship and improving quality of life in men with prostate cancer**

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## **Abstract**

**Context:** Long term survival following a diagnosis of cancer is improving in developed nations. However, living longer, does not necessarily equate to living well.

**Objective:** Systematically search and narratively synthesise the evidence from randomised controlled trials of supportive interventions designed to improve prostate cancer specific quality of life.

**Evidence Acquisition:** A systematic search of MEDLINE and EMBASE was carried out from inception to July 2014 to identify interventions targeting prostate cancer quality of life outcomes. We did not include non-randomised studies or trials of mixed cancer groups. In addition to database searches, citations from included papers were hand searched for any potentially eligible trials.

**Evidence synthesis:** A total of 2654 prostate cancer survivors from 20 eligible randomised controlled trials were identified from our database searches and reference checks. Disease specific quality of life was assessed most frequently by the functional assessment of cancer therapy-prostate questionnaire. Included studies involved men across all stages of disease. Supportive interventions that featured individually tailored approaches and supportive interaction with dedicated staff produced the most convincing evidence of a benefit for prostate cancer specific quality of life. Much of these data come from lifestyle interventions. Our review found little supportive evidence for simple literature provision (either in booklets or via online platforms) or cognitive behavioural approaches.

**Conclusions:** Physical and psychological health problems can have a serious negative impact on quality of life in prostate cancer survivors. Individually tailored supportive interventions such as exercise prescription/referral should be considered by multi-disciplinary clinical teams, where available. Cost-effectiveness data and an understanding of how to sustain benefits over the long term are important areas for future research.

**Patient summary:** This review of supportive interventions for improving quality of life in prostate cancer survivors found that supervised and individually tailored patient centred interventions such as lifestyle programmes are of benefit.

## 1. Cancer survivorship in context

Long term survival following a diagnosis of cancer is improving in developed nations.[1] The term 'cancer survivor' is an umbrella term describing the broad experience of the cancer continuum, i.e. *"living with, through, and beyond a cancer diagnosis."* This definition has been proposed by the National Consortium for Cancer Survivorship in the USA and is echoed by European cancer charities such as Macmillan. The term has evolved and disseminated into clinical practice following high profile advocates such as Dr Fitzhugh Mullan, describing his own cancer journey from a clinician's perspective in the New England Journal of Medicine, nearly 30 years ago.[2]

Living longer however, does not necessarily equate to living well. Acceptance that cancer and its treatments can have a negative long term effect on quality of life has been increasing over the past 40 years. This was first evidenced by the passage of the National Cancer Act in the USA (1971) which promoted research into meeting ongoing post-diagnosis needs. By the early 1980s new initiatives such as dedicated rehabilitation programmes directed at improving quality of life began to emerge.[3] Hence, within the survivorship agenda is an implicit undertaking to improve quality of life in those diagnosed and treated for cancer. Whereas the concept of 'quality of life' is intuitive, it is generally a personal construct and has traditionally been difficult to measure. Reliable measurement and comparison have been improved by the development and validation of generic health related quality of life tools (e.g. short-form 36, EUROQoL EQ-5D), instruments to measure quality of life across cancer in general (e.g. EORTC QLQ-C30) cancer-related fatigue (e.g. FACT-F), and disease-specific tools (e.g. FACT-P, EORTC Prostate-specific tool QLQ-PR25 for prostate cancer ). A review of tools to measure quality of life in prostate cancer survivors is freely available on the web.[4]

The organisation of medical care in Europe has typically not been as quick to adopt such paradigms in standard health care. For example, the UK government only recognised a lack of focus on the long term consequences of a cancer in its 'Improving outcomes' strategy document in 2010.[5] In recognition of this, the National Cancer Survivorship Initiative was launched, recommending that cancer be considered as analogous to living with a long-term or chronic condition.[6] Prostate cancer, in particular, fits this long-term condition paradigm: it is the main global contributor to years lived with cancer disability [7] with an estimated global prevalence of around four million men in 2012.[8]

All clinicians treating men with prostate cancer, regardless of stage, need to be aware of the issues that affect quality of life in men with prostate cancer - both immediately after diagnosis and

treatment and in the many years that follow. The relevance to a urological audience is that the urologist is often the primary (and indeed may be the only) treating physician, nevertheless, high-quality survivorship requires engagement from all involved in the care of men with prostate cancer. The aim of this manuscript is to 1) contextualise living with and beyond prostate cancer with particular regard to adverse events associated with treatment 2) review the effects of interventions that can improve prostate cancer specific quality of life and 3) highlight how care co-ordination and symptom management can be addressed by multi-disciplinary teams.

## **2. The lived experience of prostate cancer**

People surviving cancer are less likely to report favourable quality of life than individuals from the general population or patients surveyed from primary care.[9] Further, cancer survivors are significantly more likely to report being in average or poor general health (47% of survivors vs 17% of healthy participants).[10] Nearly half with common cancers (breast, bowel, prostate) will suffer from additional chronic conditions: most frequently these are arthritis, heart disease, diabetes, asthma and osteoporosis.[10] Indeed, data from the Surveillance, Epidemiology and End Results Tumour Registry (103,086 men aged 66 to 84 diagnosed with prostate cancer), reported roughly equivalent rates of prostate cancer (7.7%) and cardiovascular (7.2%) mortality.[11] At the population-level, risk of prostate cancer death is predicated upon numerous factors including the prevalence of PSA screening. Advancing age, co-morbidity and adverse effects of treatment for advanced disease are likely key determinants of non-cancer mortality.

From a psychological perspective, data from a meta-analysis indicate clinically relevant depression to be present in 17%, 15% and 18% of men before, during and after treatment for prostate cancer, respectively. Similarly, clinically relevant anxiety is high with a pre-treatment, on-treatment and post-treatment prevalence reported at 27%, 15% and 18%, respectively.[12] In advancing disease where medical or surgical castration is utilised, the risk of incident psychiatric illness (composite of depression, dementia, anxiety, insomnia, psychosis) is up to 26% over a seven year follow-up. [13] It is important to note that suicidal intent in prostate cancer survivors is associated with both physical and psychological dysfunction.[14] Hence, clinicians should be aware that as many as one in four of their patients could have clinically relevant psychological morbidity.

Without consideration of these data by the clinician responsible for primary treatment, it is easy to conceive that these issues would go unidentified and a number of men have to endure untreated

psychological distress.[15] These data underscore the importance of symptom recognition by the primary treating clinician.

### **3. Adverse effects of anti-cancer treatment**

#### *3.1 Radical therapies*

The adverse effects of surgery in the form of radical prostatectomy (RP) can be broadly categorized as complications related to function (e.g. continence, erectile) or others (e.g. anastomotic leak). Reported post-RP urinary incontinence rates range from 5 to 72%.[16] Factors including older age, higher body mass index, increasing comorbidity index, preoperative lower urinary tract symptoms, greater prostate volume, and the postoperative development of an anastomotic stricture have been associated with an increased risk for persistent incontinence.[16-18] Rates of erectile dysfunction after RP range from 31 to 86%, [16] depending on the definition of potency, the population studied, and the timeframe evaluated. Factors associated with postoperative erectile function include age, preoperative erectile function, comorbidity status, body mass index, pre-treatment PSA, the extent of nerve-sparing performed at surgery. [16, 19, 20]

Importantly, non-functional complications from RP may arise both in the perioperative period as well as during extended follow-up after surgery. Indeed, critical analysis of RP series have collectively found the procedure to be associated with an overall complication rate of approximately 10%, although the vast majority of complications are low-grade, most commonly lymphocele/ lymphorrhea and urine leak.[21] Comorbidity status, extent of disease and surgical approach have been variously associated with perioperative outcomes. Surgeon experience may also be related to complication rates.[21]

Prostatic irradiation (RT) is most commonly associated with adverse effects around late rectal function/ toxicity (i.e. increased frequency and urgency of defecation, faecal incontinence and rectal bleeding).[22] High dose RT to the rectal wall can lead to anatomical and functional damage including telangectasia, mucosal congestion, ulceration and fibrosis [23] with associated impairment of sensation, compliance and capacity. [24] Similarly, irradiation of the anal sphincter complex may impair function. As such, compared to RP, RT is more likely to induce declines in bowel function at two, five and 15 years of follow-up.[25] A recent critical review of functional outcomes reports that total urinary incontinence and other severe urinary symptoms are rare.[26] However, bothersome

storage urinary symptoms are relatively common among patients undergoing radiation therapy, and some men may also experience fatigue and erectile dysfunction.

### *3.2 Androgen deprivation therapy*

Despite its acknowledged anti-cancer benefits [27-29], androgen deprivation therapy (ADT) is associated with a range of adverse effects in survivors. These have been extensively covered in a recent review in *European Urology*. [30] Briefly, these include increased fracture risk, [31] metabolic consequences and cardiovascular events, [32-36] genital and sexual dysfunction, [37, 38] fatigue [39] and anaemia. [40] The association between ADT and cardiovascular risk remains controversial and this has been discussed elsewhere. [33, 36, 41]

## **4. Evidence acquisition**

A systematic search of the electronic databases MEDLINE (via PubMed) and EMBASE was carried out from inception to July 2014 to identify interventions targeting prostate cancer quality of life outcomes. MEDLINE search terms were prostate cancer [TIAB] AND (quality of life [TIAB]) using a randomised controlled trial (RCT) only filter. EMBASE search terms were prostate cancer AND quality of life using an RCT only filter. Eligible studies that are known to the authors but not picked up by the data base searches, were also evaluated for inclusion. We only included supportive interventions that were directed at improving a prostate cancer specific quality of life outcome in men with diagnosed prostate cancer evaluated in an RCT with a usual care comparison. We did not include non-randomised studies or trials of mixed cancer groups. In addition to database searches, citations for included papers were hand searched for any potentially eligible trials. Quality appraisal was done according to prostate cancer trial expertise and clinical judgement of the authors (led by LB). Results were screened firstly by title, then abstract and then full text in order to generate a PRISMA flow diagram of results. [42] Due to the likely heterogeneity of interventions and the non-standardised quality appraisal, a narrative synthesis rather than a quantified meta-analysis of data was performed.

## **5. Search results**

A total of 22 manuscripts from 20 trials were identified through our searches (see Figure 1), involving 2654 prostate cancer survivors. Quality of life was assessed by questionnaire in all trials, involving survivors with T stage 1-4 prostate cancer. Interventions were broadly categorised as lifestyle interventions (10 studies), educational support (five studies), enhanced standard care (three studies) or cognitive behavioural approaches (two studies). Table 1 provides a summary of included studies.

## 6. Evidence synthesis

### 6.1 Lifestyle

#### *Exercise interventions*

The last decade has seen a growing interest in interventions that improve exercise behaviour and have been hypothesized to improve clinical outcomes in men with prostate cancer.

Early pilot study data (intervention n =11, control n =10) reported that in men receiving radiotherapy for localised prostate cancer, a directly supervised (by a kinesiotherapist and physician) aerobic exercise training programme, consisting of three sessions of moderate intensity exercise for eight weeks, significantly improved FACT-P scores in the intervention group compared to controls. [43] Crucially, the mean difference between groups (14 points, SD = 10 points) exceeded the reference range which suggests clinically meaningful results (i.e. 6-9 points). [44] These effects were not however, substantiated in a later, larger RCT comparing aerobic (n=40) or resistance training (n=40) to usual care (n =41) in men scheduled to receive radiotherapy. [45] This is despite the trial reporting excellent adherence to the interventions with 88 and 83% of the sessions completed in the resistance and aerobic groups, respectively. The conflicting findings of these trials could be explained by a number of factors. First, the larger study included a wider, heterogeneous cohort of men with diagnosed stage I-IV cancers, with around 60% of the overall cohort on ADT. In addition, nearly half of the cohort was already regularly active at baseline, raising the possibility of uncertain incremental gains in these individuals from participating in the trial intervention. Another important difference is in the utilisation of the FACT-P questionnaire. The early pilot trial administered and reported data from a composite of the full FACT-G questionnaire with the additional FACT-P prostate specific subscale to give a more informed overview of quality of life, where the larger RCT reported data from the 12 item subscale only.

In one of the first RCTs of an exercise intervention involving men with prostate cancer, Segal and colleagues [46] randomised men with stage I-IV disease scheduled to receive at least 3 months of ADT to a 12 week supervised resistance exercise training programme (n= 82) or a waiting list control group (n=73). Significant differences in FACT-P mean change scores were reported at 12 weeks of follow-up (mean +2 points [SD =9 points] vs. - 3 points [SD =10 points] in the intervention and controls, respectively). Whilst this does not achieve the suggested clinically relevant threshold, planned exploratory analysis suggested that significant effects were present regardless of curative or palliative treatment intent, or duration of ADT. Further support for exercise training in men on ADT



has recently been reported by Cormie and colleagues.[47] Randomising men on ADT for at least two months (with at least 6 months planned retention) to either a 12 week supervised aerobic and resistance training programme or usual care, produced significant effects on sexual activity as measured by the EORTC QLQ-PR25 tool. Whilst this represents a novel and potentially important outcome, some caution is warranted due to the limited sample size (exercise n = 29, control n = 27). It should also be noted that there was very little improvement in sexual activity in the intervention group but rather maintenance of baseline activity over the intervention period, compared to controls who reported substantial declines.

Despite some encouraging data from supervised exercise programmes, it is unclear as to whether such interventions could be readily incorporated into service provision in secondary care. With this in mind, home based interventions have been utilised as an attempt to recreate some of the clinical benefits whilst reducing costs and resources associated with supervised programmes. The largest of these trials involved men from all disease stages (described as 'local' to 'metastatic') but with the majority treated radically.[48] Randomisation was to either a simple two page fact sheet on physical activity guidelines for adults (n = 141), self-directed exercise goal setting, barrier identification and planning (n = 141) or telephone counselling assisted exercise goal setting, barrier identification and planning (n = 141). After three months of follow-up, no effect on prostate cancer specific quality of life was reported. Critically, only 13.6% of participants in the intervention groups had reported completing the intended goal setting and planning activity, rendering a conclusion of no intervention effect as uncertain. It is also salient to note recruited participants were already physically active for an average of at least two hours per week at baseline, raising the potential for ceiling effects this trial cohort. Home based approaches in men on ADT have also been attempted with similar null effects on quality of life.[49] This trial suffered from a 34% drop out over the 16 week intervention period, rendering a high risk of bias around these data.

### *Diet*

Modifications to dietary behaviours have generated interest in the research community through potential beneficial impacts on a wide range of clinically relevant outcomes in prostate cancer from disease progression [50] to mitigating the side effects of ADT. [51]

A supervised programme of 11 weekly cooking classes (2.5 hours each) encouraging the preparation of plant based meals, fish, soy and avoiding meat and dairy products, reported a significant effect on FACT-P in men with biochemical recurrence after radical therapy.[52] It is unfortunately not possible

to ascertain whether this difference was clinically meaningful in effect size, as no point estimates or measures of variation were included in the manuscript. These data should be regarded as preliminary only, given the small sample (n=36). Some support for soy supplementation in the diet of men on ADT has been reported by Vitolins and colleagues [53] in a trial evaluating soy protein supplementation (20 g with 160 mg isoflavones, n = 30), versus Venlafaxine (75mg once daily, n =30), versus combined soy and Venlafaxine (n =30) or milk powder placebo (n =30). The authors reported a significant and clinically relevant difference in FACT-P after 12 weeks in men taking soy protein (mean = 113 points, SE = 6 points) versus men who did not take soy protein (mean = 104 points, SE = 6 points). Whilst this is positive, it should be noted that the analysis presented pooled data from both the soy only and soy with Venlafaxine arms. Hence, it is not possible to untangle the possible effect(s) of each individual intervention.

Importantly, other elements of dietary change designed to mitigate adverse effects of radical treatment, have not produced improvements in quality of life. No significant effect was reported in survivors with stage I-III disease [54] scheduled to undergo seven weeks of radiotherapy (in combination with either high dose brachytherapy or proton therapy) who were randomised to receive advice to reduce lactose consumption and choose foods with soluble fibre (n =64) or standard care (n =66). Discrepancies in findings across these three trials could be explained by the different primary treatment regimens in these studies, the impact of pharmacological agents in combination with diet changes, or could again be a reflection of more intensive intervention delivery in the pilot RCT.

#### *Exercise and diet*

Recent data from an evaluation of an individually tailored, combined exercise and dietary advice intervention has demonstrated novel improvements in quality of life in men with advanced disease on planned long term retention on ADT.[55] Specifically, men were randomised to usual care (n = 50) or to receive tapered supervised aerobic and resistance exercise along with dietary advice encouraging reduction of saturated fat and refined carbohydrate and increase of dietary fibre intake (n = 50). Crucially, all participants were not active at baseline, enhancing the generalisability of these data (the large majority of men with prostate cancer are not regularly active).[9] Clinically relevant improvements in FACT-P were reported at the end of the intervention at 12 weeks of follow (p = 0.001, mean difference = 8.9 points). However, these benefits were not sustained at six months post-intervention when support was withdrawn, and notably trial retention dropped from 85 to

68%. These data underscore the importance of sustainability associated with lifestyle-based interventions directed towards improvement in prostate cancer specific quality of life.

With the supportive evidence from exercise interventions, combining them with dietary advice would appear to be a promising strategy for improving prostate cancer specific quality of life. In addition, exercise interventions could positively effect a range of other important patient outcomes. A systematic review of this topic is currently underway.[56] To ensure sustainability of the benefits, on-going support from dedicated staff and a mix of supervised and independent intervention components is required.[57] The treating clinician could play an important role in directly advocating such programmes and arranging referral. These interventions are comparatively low risk to participants: the major obstacle is likely the cost of physical infrastructure (although this need not be based in secondary care, this could be community based) and staff time.

## **6.2 Educational support interventions**

Given the numerous adverse effects associated with primary treatment for prostate cancer, the potential impact of clinical applications of educational support has been evaluated using several approaches.

### *Multi-disciplinary approaches*

Both pilot (n = 57) and larger trial (n =250) results of group based multi-disciplinary interventions (facilitated by a health psychologists, medical oncologists, urologists, dieticians and psychiatrists) reported small benefits on FACT-P outcome (effect size=0.1) at six months [58] or no interaction effect on the UCLA PCI urinary, bowel or sexual function at 12 months, [59] of follow-up. Recent data from Dieperink and colleagues [60] is more positive. Prostate cancer survivors treated with radiotherapy and ADT were assigned to outpatient, mixed nurse and physical therapist led counselling (n=79) or usual care (n=82). The nursing component provided psychological support and identified disease specific problems for the survivor and their spouse, whilst the physical therapist worked to improve pelvic floor muscle function and general physical activity. The urinary irritative sum-score and hormonal domains of the EPIC questionnaire significantly improved in the intervention vs controls at 20 weeks of follow-up (effect size = 0.34, 0.4 and 0.19, respectively). This intervention likely succeeded where earlier trials have not, by involving a smaller number of health professionals and allowing more focused tailoring of the intervention. Such approaches have been supported by prostate cancer survivors in qualitative investigation following rehabilitation interventions previously. [61]

### *Literature provision and online resources*

Two pilot trials evaluating provision of an educational booklet or referral to an online support group suggested a positive beneficial effect in disease specific quality of life. However, authors of the booklet evaluation did not report interaction effects or point estimates in their analysis of FACT-P scores, choosing to separately analyse pre and post test scores in the intervention and control group. [62] The online support group seemed to initially improve EPIC scores over six weeks but these beneficial effects were transient, returning to baseline just two weeks later. [63] Hence, there is uncertainty around meaningful clinical benefit from these early data.

As with exercise interventions, the individually tailored approach of Dieperink and colleagues offers promise for prostate cancer survivors. Further independent observations offering supportive data alongside cost effectiveness evidence is now required.

### **6.3 Enhanced standard care**

Enhancing existing features of prostate cancer care could lead to better outcomes for survivors. For example, men who engage and participate in treatment decision making are considered to experience better satisfaction with overall care. To evaluate if this extended to disease specific quality of life, Hack and colleagues [64] evaluated the provision of audiotapes of treatment consultations with oncologists to men with stage I-IV disease. Men were randomised to no audio taping (n = 113), audio taping performed but no tape provided (n = 98), audio tape provided (n = 120) or tape provided on patient request (n = 94). No effect on quality of life was reported at 12 weeks of follow-up. This large RCT suggests there is no clinical benefit of audiotaping treatment consultations.

Pelvic floor muscle training is an important element of post radical prostatectomy rehabilitation. Evaluation of enhancing recovery with the aid of a physiotherapist (n=38) compared to standard care (n=42) did not result in any disease specific quality of life gains in men with stage I-III disease.[65, 66] However, some potential for type II error must be considered in this trial as only 50% of intervention participants attended the physiotherapist led group training sessions.

Tailored, nurse-led initiatives have reported more promising data. Giesler and colleagues [67] designed an intervention to enhance quality of life using the 'proximal: distal' framework (i.e. identification of clinical symptoms with the downstream intention effecting life satisfaction). Prostate cancer specific issues (e.g. urinary dysfunction, cancer worry, fatigue etc.) were identified

with matched interventional strategies e.g. Kegel exercises for urinary incontinence. Patient-spouse dyads in the intervention arm met once each month for 6 months with a nurse (twice in person and 4 times by telephone). At 12 months of follow-up, improvement in sexual limitation ( $P=0.02$ , effect size 0.5) and cancer worry ( $P=0.03$ , effect size 0.51) were reported in the intervention group, compared to controls. These data add further support to the evidence for tailored interventions delivered by dedicated staff to improve prostate cancer specific quality of life.

#### **6.4 Cognitive behavioural approaches**

Two studies have evaluated cognitive behavioural approaches in survivors with localised disease. The first, larger trial, [68] randomised men scheduled to undergo radical prostatectomy to individual sessions of cognitive behavioural stress management ( $n=53$ ) with the majority of the 90 minute content focused on relaxation skills and guided imagery, supportive attention ( $n=54$ ) or standard care ( $n = 52$ ). No effect on UCLA PCI outcomes was reported after up to 12 months of follow-up. The later, smaller study ( $n=60$ ), assessed the potential of a cognitive-behavioural group intervention that addressed the psycho-sexual adjustment of men up to five years post radical prostatectomy. [69] Disease specific quality of life was evaluated using the prostate cancer quality of life scale. The authors indicated the intervention improved sexual confidence, intimacy, masculine self-esteem and satisfaction with orgasm in a hierarchical regression. However, it is difficult to understand the clinical relevance of this data, as post-intervention means and 95% confidence intervals were presented only for the cohort as a whole, rather than according to randomisation. As such, it appears that currently, there is little evidence that cognitive behavioural approaches can be recommended in clinical practice for improving prostate cancer specific quality of life.

#### **7. Survivorship care coordination and the interface with primary care**

Coordination of care for prostate cancer survivors is essential to optimize quality of life and promote efficient health care utilization although no randomized trials currently examine this in prostate cancer specifically. However, fragmented, poorly coordinated prostate cancer survivorship care may be associated with duplicate services e.g. PSA testing and greater spending, particularly amongst those treated with radical therapy.[70] A lack of agreement regarding roles and responsibilities among patients, primary and specialty care providers during survivorship can exacerbate the issue.[71, 72] The Institute of Medicine formally recognized the need to address coordination of survivorship care nearly a decade ago by recommending provision of a survivorship care plan. This includes a treatment summary and follow-up care plan for cancer survivors as they transition across the primary/ specialty care interface. This standard will require an institution's cancer committee to

develop and implement a process for disseminating comprehensive care summaries and follow-up plans to cancer patients completing treatment with the hope of improving patient-centred care and outcomes. However, the evidence to support formalized cancer survivorship care plan development and provision are mixed and concerns remain regarding their implementation (e.g., reimbursement, maintenance, contents).[73] According to a recent nationally-representative survey in the USA, primary care providers who received a survivorship care plan from an oncologist were nine times more likely to report survivorship discussions with cancer survivors. [71] However in the same study, less than 5% of oncology providers routinely issued a written survivorship care plan, and survivorship care discussions among primary care providers and patients are still rare.

The American Cancer Society Prostate Cancer Survivorship Care Guidelines [74] support the IOM recommendations that cancer specialists provide survivorship care plans including treatment summary and follow up recommendations to primary care providers. The guidelines also highlight some practical shared care recommendations to optimize longitudinal prostate cancer survivorship care and quality of life. Firstly, they recommended specialist provision of a post-treatment patient-reported measure of side effect burden (e.g., the one page Expanded Prostate Cancer Index Composite for Clinical Practice) [75] to primary care providers to facilitate longitudinal self- and medical management efforts. A second recommendation was a minimum of annual assessment of late and long-term health-related quality of life effects including the psychosocial effects of a cancer diagnosis. A third was inter-professional shared decision-making among the primary and specialty care providers to tailor roles and responsibilities for central tenets of survivorship care including health promotion, prostate cancer surveillance, screening for second primary cancers, long-term and late effects assessment and management based on the patient's condition and resources/expertise in their primary care setting. The latter is especially important given previous disagreement among the primary care and oncology communities regarding survivorship follow up care coordination and responsibilities.[76] These guidelines were recently endorsed by the American Society for Clinical Oncology with minor modifications.

## **8. Review limitations**

This manuscript specifically targeted randomized clinical trials addressing prostate cancer quality of life outcomes finding several educational, lifestyle, and behavioural interventions that may improve disease specific quality of life. Other behavioural, medical and surgical approaches to symptom and side effect management are covered elsewhere [74] and were not the focus of this review.

Nevertheless, more work needs to be done in this field to build the high level evidence base

necessary to support men, their partners and clinicians as they survive prostate cancer. A lack of consistent instrument selection in the included studies makes evidence synthesis challenging with respect to which intervention and instrument outcomes are most relevant to individual survivors (e.g., urinary, bowel, sexual, psychosocial, merits of exercise, etc.). Consensus on which instruments are most informative would likely be an informative next step. The FACT-P tool was the most frequently used in the studies included in the present review. A recent international working group advocated the Expanded Prostate Cancer Index Composite Short Form for assessing men with localised prostate cancer. [77]

## **9. Research recommendations**

The treating clinician could play a role in directly advocating supportive programmes to survivors and leading the multi-disciplinary team in the referral process. Qualitative evaluation of how some of the interventions covered in this review could be introduced into standard care (e.g. in the NHS) would be an ideal way to identify barriers, facilitators and map roles and responsibilities for care teams looking to deliver evidence based survivorship care. Multi-centre, randomised clinical trials of such pragmatic complex interventions would appear to be the best way of evaluating effectiveness in the long term. Crucially, cost effectiveness data have not been generated for these programmes, and should be collected in parallel during clinical studies. These data will play an important role in the dialogue with commissioners, insurers and other payers.

## **10. Conclusions**

Prostate cancer is the main global contributor to years lived with cancer disability. Primary treatments can often leave men with serious ongoing health problems, both physical and psychological, which adversely affect quality of life. Supportive interventions which incorporate direct interaction with specialist health professionals and feature individually tailored prescriptions have shown promise for improving disease specific quality of life. Much of the data in this review comes from lifestyle interventions. Whilst these data are promising, these programmes are non-standard for most clinical teams in terms of delivery. As such, further understanding of how these programmes can be implemented in current practice and how patient engagement and adherence can be maximised, is required. These initiatives are likely to be of low risk in terms of potential harm to participants.

## Figure Legends:

Table 1: Summary of table of included randomised controlled trials

Figure 1: PRISMA flow diagram of search results.

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**Author contributions:** Liam Bourke had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis.

**Study concept and design:** Bourke, Penson.

**Acquisition of data:** Bourke

**Analysis and interpretation of data:** Bourke, Skolarus, Rosario, Boorjian, Resnick, Briganti, Klotz, Penson.

**Drafting of the manuscript:** Bourke, Skolarus, Rosario, Boorjian.

**Critical revision of the manuscript for important intellectual content:**

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