INCREASING THE IMPLEMENTATION OF EVIDENCE BASED CARE FOR HEAD AND NECK CANCER PATIENTS

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BPsyc (Hons I)

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(Clinical Psychology)

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Statement of Originality

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LIST OF PAPERS INCLUDED AS PART OF THIS THESIS

Paper One: McCarter, K., Baker, A. L., Britton, B., Wolfenden, L., Wratten, C., Bauer, J., Halpin, S., Beck, A., Carter, G., Leigh, L., Oldmeadow, C. Smoking, drinking and depression: Comorbidity in head and neck cancer patients undergoing radiotherapy. *Under Review.*

Paper Two: McCarter, K., Britton, B., Baker, A. L., Halpin, S., Beck, A., Carter, G., Wratten, C., Bauer, J., Booth, D., Forbes, E., Wolfenden, L. Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review protocol. BMJ Open, 2015;5:e008277. doi: 10.1136/bmjopen-2015-008277.

Paper Three: McCarter, K., Britton, B., Baker, A. L., Halpin, S., Beck, A., Carter, G., Wratten, C., Bauer, J., Booth, D., Forbes, E., Wolfenden, L. Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review. *Under Review.*

Paper Four: Britton, B., McCarter, K., Baker, A., Wolfenden, L., Wratten, C., Bauer, J., Beck, A., McElduff, P., Halpin, S., Carter, G. Eating As Treatment (EAT) study protocol: A stepped-wedge, randomised controlled trial of a health behaviour change intervention provided by dietitians to improve nutrition in patients with head and neck cancer undergoing radiotherapy. BMJ Open, 2015;5:e008921. doi: 10.1136/bmjopen-2015-008921.

Paper Five: McCarter, K., Baker, A., Britton, B., Beck, A. K., Carter, G., Bauer, J., Wratten, C., Halpin, S., Holliday, E., Oldemeadow, C., Wolfenden, L. Effectiveness of clinical practice change strategies in improving dietitian care for head and neck cancer patients according to evidence based clinical guidelines: A stepped wedge randomised controlled trial. *Under Review.*

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ADDITIONAL PUBLICATIONS AND PRESENTATIONS

Papers:

Stuart, A., Baker, A. L., Bowman, J., **McCarter, K.,** Denham, A., Lee, N., Colyvas, K., Dunlop, A. Protocol for a systematic review of psychological treatment for methamphetamine use: an analysis of methamphetamine use and mental health symptom outcomes. *Accepted for publication. BMJ Open.*

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International Congress of Behavioral Medicine, Melbourne. 7-10 December 2016.
Britton. B., Beck, A., **McCarter, K.,** Baker, A., Wolfenden, L., Wratten, C., Bauer, J., McElduff, P., Carter, G**.**
Eating as Treatment (EAT): A health behaviour change intervention to improve treatment outcomes for head and neck cancer patients undergoing radiotherapy.

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Patient, clinician and systems change: Using cognitive and behavioural strategies to improve treatment outcomes for head and neck cancer patients undergoing radiotherapy.

International Congress of Behavioral Medicine, Melbourne. 7-10 December 2016.

McCarter, K., Britton. B., Baker, A., Wolfenden, L., Wratten, C., Bauer, J., Beck, A., McElduff, P., Halpin, S., Carter, G**.**
Co-occurring depression, tobacco and alcohol use in a sample of head and neck cancer patients undergoing radiotherapy.

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Eating As Treatment (EAT): A health behaviour change intervention to improve treatment outcomes for head and neck cancer patients undergoing radiotherapy. In: *Asia-Pacific Journal of Clinical Oncology.* Special Issue: *Hunter Cancer Research Alliance Annual Symposium 2016*, November 2016. doi: 10.1111/ajco.12617

Cancer Institute NSW Innovations in Cancer Treatment and Care Conference, Sydney. October 2015.
McCarter, K., Wolfenden, L., Baker, A., Britton, B., Beck, A., Carter, G., Bauer, J., Wratten, C., McElduff, P., Halpin, S. A clinical practice change intervention to increase dietitian provision of routine depression screening and appropriate referral for psychosocial support in head and neck cancer patients.

Behavioural Research in Cancer Control, Sydney. May 2015.
McCarter, K., Forbes, E., Baker, A., Britton, B. Beck, A. Carter, G., Bauer, J., Wolfenden, L., Wratten, C., McElduff, P., Bonevski, B., Halpin, S. Smoking during radiotherapy: Rates of continued tobacco smoking in a sample of head and neck cancer patients.

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LIST OF ABBREVIATIONS

HNC	head and neck cancer
RCT	randomised controlled trial
SCC	squamous cell carcinoma
US	United States
HPV	human papilloma virus
RT	radiotherapy
QoL	quality of life
HRQoL	health related quality of life
NCCN	National Comprehensive Cancer Network
CO	carbon monoxide
AUDIT	Alcohol Use Disorders Identification Test
PHQ	Patient Health Questionnaire
MDE	major depressive episode
HREC	Human Research Ethics Committee
ATSI	Aboriginal and Torres Strait Islander
PEG	prophylactic percutaneous endoscopic gastrostomy
NGT	nasogastric tube
PPM	parts per million
FTND	Fagerstrom Test for Nicotine Dependence
WHO	World Health Organisation
SD	standard deviation
CBT	Cognitive Behaviour Therapy
MI	Motivational Interviewing

ABBREVIATIONS

PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
DT	Distress Thermometer
CENTRAL	Cochrane Central Register of Controlled Trials
HADS	Hospital Anxiety and Depression Scale
GRADE	Grades of Recommendation, Assessment, Development and Evaluation
EPOC	Effective Practice and Organisation of Care
EPHPP	Effective Public Health Practice Project Quality Assessment Tool
DB	Distress Barometer
SIPP	Screening Inventory Psychosocial Problems
DIT	Distress and Impact Thermometer
EAT	Eating As Treatment
PG-SGA	Patient-Generated—Subjective Global Assessment
TROG	Trans-Tasman Radiation Oncology Group
EORTC QLQ-C30	The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire
ARM-5	Agnew Relationship Measure—Five Item Version—Patient Rated
NRT	nicotine replacement therapy
CER	comparative effectiveness research
OMSC	Ottawa Model of Smoking Cessation

Note. This list represents the abbreviations used in the main text of the thesis.

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INCREASING THE IMPLEMENTATION OF EVIDENCE BASED CARE FOR HEAD AND NECK CANCER PATIENTS

SYNOPSIS

Patients with head and neck cancer (HNC) have a significant mortality rate and unique challenges associated with the malignancy and its treatment. One component of this disease burden is the prevalence of modifiable health risk behaviours and affect, in particular, tobacco smoking, harmful alcohol consumption and depression. Additionally, the provision of evidence based care for HNC patients by clinicians is an important priority. Despite this, there are existing gaps regarding the occurrence and comorbidity of health risk behaviours and affect components in HNC and effective approaches to increase the provision of evidence based care for HNC patients in cancer settings. To address these evidence gaps, the aims of this thesis were to:

1. Describe the rates and co-occurrence of tobacco smoking, alcohol use and depressive symptoms in a sample of HNC patients undergoing radiotherapy;

2. Systematically review the literature to determine the impact of interventions to improve clinician provision of screening and appropriate referral of patients with cancer for distress;

3. Assess the effectiveness of clinical practice change strategies in improving dietitian implementation of best practice guideline recommendations for HNC patients;

4. Systematically review the literature to examine the effectiveness of smoking cessation interventions on smoking cessation rates in adult HNC patients.

These four aims have been addressed in a series of studies that includes: a cross-sectional study of 307 HNC patients' baseline assessments from an intervention trial involving four hospitals across Australia; a systematic review describing the results of

five studies aimed at improving the rates of distress screening and/or referral in cancer patients; a multi-site stepped-wedge randomised controlled trial (RCT) including clinical practice change strategies; and a systematic review that presents the current evidence for smoking cessation interventions in HNC patients.

The work included in this thesis has contributed to addressing evidence gaps and advancing research in the field in a number of ways. Firstly, the findings include current rates of co-occurring health risk behaviours and affect factors in HNC as well as some of the first evidence for the prevalence of co-occurrence of these problems in this population. Secondly, despite the high prevalence of these issues in HNC, my systematic review findings highlight the sub-optimal level of evidence based care delivery for distress in oncology and the astounding lack of evidence based treatments for smoking cessation in this cancer subgroup. Finally, the clinical practice change strategies employed in the multi-site stepped-wedge RCT is the first known effective HNC implementation intervention for improving care according to dietetic guidelines.

Overall, this thesis has identified a need to increase the provision of evidence based care to address high prevalence health risk behaviours and depression in patients with HNC and has trialled an effective approach to improving best practice care within oncology dietetic services. Future research considerations include identification of the specific support strategies that increase the provision of best practice care for HNC patients, implementation of multiple guidelines corresponding to co-occurring issues and sustainability of such approaches.

INTRODUCTION: BURDEN OF DISEASE, HEALTH RISK BEHAVIOURS AND CARE FOR HEAD AND NECK CANCER PATIENTS

INTRODUCTION: BURDEN OF DISEASE, HEALTH RISK BEHAVIOURS AND CARE FOR HEAD AND NECK CANCER PATIENTS

Epidemiology

Malignancies of the nasopharynx, oropharynx, oral cavity, larynx, or hypopharynx are collectively known as Head and Neck Cancers (HNC), and are the world's sixth most common cancer (1). Almost all of these epithelial malignancies are squamous cell carcinomas (SCC) of the head and neck (2). This group of cancers represents approximately 6% of all cancer cases and accounts for an estimated 650 000 new cancer cases and 350 000 cancer deaths worldwide every year (2). High risk regions for oral cavity cancer include Melanesia and southcentral Asia, western and southern Europe, and southern Africa, and for laryngeal cancer southern and eastern Europe, South America, and western Asia (3). In Australia, the estimated number of new cases of HNC diagnosed in 2017 is 4 956 (3.7% of all new cancer cases) (4).

The median age for diagnosis is in a patient's early 60s (5). HNC has been associated with low socioeconomic status, diagnosis at a younger age, more frequent diagnosis at advanced stage and lower average survival across all age groups (6). Approximately two-thirds of patients with HNC present with advanced stage disease, frequently involving regional lymph nodes (2). Distant metastasis at initial presentation is uncommon, present in about 10% of patients (5).

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HNC related burden of disease

HNC is responsible for a significant mortality burden, with the rate ranking seventh worldwide (1). Based on Surveillance Epidemiology and End Results data, the five-year survival for all stages combined is about 60% and survival is worse for particular primary sites such as the hypopharynx (5). Approximately 1 026 deaths in Australia in 2017 will be attributable to HNC, accounting for 2.1% of all cancer deaths (4).

Evaluating the health care costs associated with HNC diagnosis and treatment is complex as the malignancy can involve multiple sites, treatment can include different modalities and management requires a multidisciplinary team due to the unique challenges for this population. A systematic review published in 2014 (7) was unable to identify any studies incorporating both direct and indirect costs from HNC. However, with regard to direct costs, the review identified high direct costs to payers, with one study estimating the national yearly expenditures in the United States (US) totalled US $16.47 billion. One study reported that earnings lost as a measure of productivity due to HNC in 2010 was US $3.4 billion. No comparative Australian data on health or societal costs associated with HNC are available.

HNC and its associated treatments affect many aspects of daily functioning and general wellbeing. These include difficulties with eating and swallowing, speaking, pain and disfigurement (8). The Centres for Disease Control and Prevention in the US published a report in 2005 based on data from 1997-2001 and found that cancers of the lip, oral cavity, pharynx, and larynx were responsible for 131 479 years of potential life lost annually (9). A 2006 study (10) reported on the burden of major cancers due to smoking in Korea and included data on cancers of the lip, oral cavity, pharynx and larynx. The

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number of disability-adjusted life years lost (sum of the years of life lost due to premature mortality from a disease and the years of healthy life lost as a result of disability) for these cancers was reported as 180.6 person-years per 100 000 people for 2001. While these estimates were lower than those for lung, trachea and bronchus cancer, the burden attributed to cancers of the head and neck remained significant at more than twice that of smoking related kidney and urinary cancer (10).

Risk factors for HNC

The majority of HNCs worldwide remain attributable to tobacco and alcohol use, with human papilloma virus (HPV) newly identified as a causal factor (11-13).

Tobacco

The International Agency for Research on Cancer classifies tobacco smoking as a group 1 carcinogen for both the oral cavity and the pharynx (14). A meta-analysis by Gandini et al. noted a relative risk of 6.98 for laryngeal cancer, 6.76 for pharyngeal and oropharyngeal SCC and 3.43 for oral cavity SCC, among current tobacco smokers compared with nonsmokers (15). HNC due to smoking appears to be dose dependent and correlates with daily or cumulative cigarette consumption (16).

Alcohol

Alcohol is an independent risk factor for HNC. Recent meta-analyses have estimated that the relative risk for head and neck SCC is 1.3 for 10 grams of ethanol per day compared with 13.0 for 125 grams of ethanol per day (17). Studies of nonsmokers note both a strong association and a dose-response relationship between alcohol consumption and oral cavity/pharyngeal SCC (18). The underlying carcinogenic mechanisms have not been established, however, several have been proposed. Ethanol is metabolised into acetaldehyde, which is a recognised carcinogen, alcohol beverages may contain

aldehyde and other carcinogenic contaminants and nutritional deficiencies may contribute to an increased risk in heavy drinkers (19).

Interaction

The combination of cigarette smoking and alcohol consumption has a multiplicative effect. The reported relative risk for head and neck SCC among heavy users of tobacco and alcohol is 15 or greater (18). Large scale multicentre studies, as well as pooled analysis of case-control studies have attributed more than half of oral and oropharyngeal cancer cases to tobacco and/or alcohol (20-22).

HPV

According to the International Agency for the Research on Cancer monograph, HPV fulfils the criteria for causality of oropharyngeal cancer (23). Recent evidence has demonstrated that HPV is involved in up to 25% of HNCs, particularly in the oropharynx where it can account for up to 60% of such subtype cancers (23-25). However, smoking and alcohol use remains common in HPV associated HNC. Snijders et al. (26) reported a large proportion of HPV- positive cases in their study had exposure to tobacco; 28.6% were heavy smokers (>20 cigarettes/day), and 50% were former smokers. Gillison et al. (27) reported that 90% of the patients with HPV-positive HNCs in their study were smokers and heavy drinkers.

Treatment

Treatment decisions in HNC are often complex, involving numerous specialists, including head and neck surgeons, medical oncologists, radiation oncologists, radiologists, plastic surgeons, dietitians and dentists. Clinical factors including primary tumour site, stage and resectability, and patient factors including swallowing and airway issues, desire for organ preservation, and comorbid illnesses are used to guide

appropriate management. Surgery and radiotherapy (RT) are the main treatment approaches for HNC. Surgery can be limited by the extent of the area of the malignancy and the goal of organ preservation (28). RT is an integral component of primary or adjuvant treatment for HNC. RT alone has high tumour control and cure rates for certain HNCs and advances in imaging and intensity-modulated RT have improved management approaches (28).

RT treatment outcomes – Treatment response, survival and quality of life

Key RT treatment outcomes in HNC are treatment response (such as tumour control) and survival. Additionally, improvement in survival rates for HNC in the last decade have led to increased focus on the importance of quality of life (QoL) as a patient reported outcome (29, 30). QoL is particularly important for HNC patients as they suffer from speech, eating and respiratory difficulties, as well as the adverse psychological effects of loss of function and change in body image (31). There are a number of factors that may influence RT treatment outcomes and QoL for HNC patients. Due to the causal association and modifiable nature of tobacco smoking and alcohol use, these are two integral factors to examine in HNC research. Investigating depression in HNC is an additional key factor that influences RT treatment outcomes and should also be a focus due to the likelihood of co-occurrence with these behavioural factors (smoking and alcohol use) and their reported high prevalence in this cancer population. According to the excessive appetite model of addiction, this clustering is likely to occur due to the appetitive nature of substance use and its reinforcing interaction with depression (32).

Tobacco

Estimates of continued tobacco use in this population vary, with evidence from observational and intervention studies reporting between one third and 75% of HNC patients continue to smoke after diagnosis (33-38). There is yet to be a systematic review published on the effect of continued tobacco smoking on tumour response or survival in HNC patients. However, in a longitudinal study with up to eight-year follow-up, Choi et al. (38) found that smoking status after a cancer diagnosis predicted overall mortality and cancer-specific mortality in 590 newly diagnosed HNC patients. Compared to never-smokers, continuing smokers have the highest hazard ratio of overall mortality followed by quitters and former smokers. A number of other key studies have demonstrated links between continued smoking and poorer tumour response, survival and poorer quality of life.

In 1993, Browman et al. (34) studied the smoking habits of 115 HNC patients undergoing RT. The main outcomes for this study were treatment response and survival. Among the 53 patients who continued to smoke during RT, 24 (45%) had a complete response (no clinical indication of disease) compared to 46 (74%) of the nonsmokers (those who abstained during RT) (p=.008). The two-year survival rate was 66% in the nonsmokers and 39% in the smokers (p=.005). Included in the regression model for survival were known prognostic variables: age, tumour stage, tumour site, treatment group and smoking status during treatment. Smoking during RT was the only significant variable independently associated with survival, with patients who continued to smoke having poorer two-year survival (p=.002). The number of years smoking was identified as an additional factor associated with survival (p=.033). However, a subsequent follow-up study by the same authors did not replicate these findings (40).

In 2011, Chen et al. (41) re-examined this issue by investigating the effect of continued smoking during RT in a sample of HNC patients. Persistent smokers ($n = 101$) were matched to controls ($n = 101$) who had quit smoking before treatment. Five-year overall survival rates were 23% and 55% respectively ($p < .001$). Unfortunately, this study was limited by retrospective analysis. Nevertheless, the data showing differing prognoses among active and former smokers provides cause for further investigation in this area.

In addition to survival, continued smoking may also affect overall QoL in HNC patients. In a cross-sectional survey, Duffy et al. (31) found that smoking negatively influenced QoL scores in a sample of 81 HNC patients. Despite the potential treatment effects of continued smoking as well as the reasonable hypothesis that tobacco use would negatively affect QoL, the association has received little research attention in this population. Smoking is a key risk factor for developing HNC, is pervasive and has negative effects on treatment outcomes. Clarifying the rates of continued smoking and the level of smoking cessation care provided to this population is important when it comes to considering quality of care for the HNC population.

Alcohol use

Due to the etiologic relationship between alcohol use and HNC, continued alcohol use in this population has received some attention. It has been reported that a substantial proportion of this patient population, ranging from 37% to 54% continues to consume alcohol after diagnosis and approximately 16% of these patients continue to drink hazardously (33, 42). In addition to having a carcinogenic effect, alcohol use is often the cause of significant comorbidities such as secondary cancers and has been associated with poorer tumour response, decreased survival rates and reduced QoL in HNC patients (42-45).

It has been suggested that the association between continued alcohol use during RT and poorer tumour response is not just a function of the synergistic effect with comorbid smoking. Potential explanations offered in the literature are biologically aggressive tumours and resistance to RT (46). When alcohol interferes with the cancer cell undergoing RT, cellular mutations may occur, such as p53 mutations (47, 48). Cancer cells with these mutations become more aggressive and consequently have a resistance to RT (49). Some retrospective studies have shown that alcohol use is associated with poorer tumour response, however the relationship with QOL is less clear. Fortin et al. (44) conducted a retrospective study in 2009 to evaluate the prognostic value of smoking and drinking status in 1871 patients with HNC. Drinking alcohol was associated with inferior local control (the arrest of cancer growth at the site of origin; $p = 0.03$). For never, former, and active drinkers, the five-year local control and survival were 77%, 74%, and 70% ($p = 0.0001$) and 70%, 58%, and 56% ($p = 0.0002$), respectively.

Deleyiannis et al. (50) identified the association between alcohol consumption and survival for 649 patients with HNC. The five-year survival estimate for those classified by the Michigan Alcoholism Screening Test as 'abstinent alcoholics' (57.1%) was significantly greater ($p = .016$ by chi-square test) than for 'alcoholics currently drinking' (40.9%). This difference remained significant after adjustment for other factors including site and anatomical stage of cancer.

Ribeiro et al. (51) examined the prognostic significance of comorbid conditions, including excessive alcohol intake in a cohort of 110 patients with SCC of the tongue or

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floor of the mouth who were admitted to a tertiary cancer hospital between 1990 and 1994, and who underwent surgery. Daily consumption of alcohol, as measured by the National Cancer Institute index, was independently predictive of five-year survival (p=.008).

Existing literature as to whether continued alcohol use is detrimental to the QoL of HNC patients is scarce. Potash et al. (42) examined the association between alcohol consumption (as measured by the Michigan Alcoholism Screening Test) and health related quality of life (HRQoL) one year after diagnosis in patients with HNC. HRQoL was measured by the Head and Neck Cancer Inventory, a well validated survey which measures the severity and frequency of HNC-specific problems, patients' perception of their eating and overall QoL. Almost half of the 283 HNC patients in this study continued drinking alcohol 12 months after diagnosis. However, neither alcohol abuse status nor continued alcohol use was independently associated with HRQoL.

In contrast, Sehlen et al. (45) conducted a study to assess which sociodemographic variables predict QoL after RT in patients with HNC. HNC patients ($n = 83$) completed the Functional Assessment of Cancer Therapy-General questionnaire, which was developed to assess cancer-specific aspects of HRQoL, at the beginning, end and six weeks after treatment. A cutpoint defined patients with high and low QoL. A logistic regression model was used to evaluate which variables at the beginning of treatment determined low QoL after RT. Five sociodemographic variables including alcohol abuse predicted low QoL ($p = 0.025$). There is an established causal relationship between alcohol use and HNC, the existing evidence suggests high rates of continued use and this has a potential negative effect on key treatment outcomes. There is a need for more

current reporting on the prevalence and pattern of alcohol use in HNC patients and investigation into treatment for this health behaviour.

Depression

Distress in cancer patients may be associated with non-adherence to treatment, poorer QoL and may negatively impact survival (52, 53) as well as increase treatment burden to the oncology team and health system (54). The US National Cancer Comprehensive Network (NCCN) defines distress as "an unpleasant experience of an emotional, psychological, social or spiritual nature, that interferes with the ability to cope with cancer treatment, which extends along a continuum from common normal feelings of vulnerability, sadness and fear, to problems that are disabling such as depression, anxiety, panic and feeling isolated or in a spiritual crisis" (52). Specifically, psychological distress such as depression and anxiety can arise in response to cancer related factors such as diagnosis and cancer progression, pain and adverse effects of treatment (55). Living with and being treated for cancer creates a 'new normal' for cancer patients and this brings with it new living conditions and symptoms (56). Patients with cancer may also have pre-existing mental health problems that contribute to increased risk of psychological distress (55). HNC patients exhibit relatively high rates of mental illness, particularly depression (54, 55). The current literature indicates that the prevalence of depression in HNC patients ranges from 22% to 57% (33, 59).

The majority of the literature addressing the association between depression and survival in cancer includes heterogeneous cancer types. A number of reviews have been conducted demonstrating the relationship between depression and cancer mortality. A review conducted by Archer et al. in 2008 (59) found a general trend of increased mortality in patients with chronic depression. Of the four studies that used diagnostic

criteria (60-63), two showed a significant impact of a depressive disorder on cancer

mortality. Of the 15 studies measuring depressive symptoms using validated

questionnaires, nine showed a significant impact of depressive symptoms on mortality.

A review and meta-analysis by Pinquart et al. in 2010 (64) analysed associations

between depression and mortality of cancer patients by integrating the results of 105

samples derived from 76 prospective studies. The authors found that depression

diagnosis and higher levels of depressive symptoms predicted elevated mortality. A

review by Spiegel and Giese-Davis (68) that aimed to disentangle the relationship

between depression and cancer progression and mortality identified three reasons why

depression may enhance mortality risk in cancer patients. First, depression may have a

pathophysiological effect via neuroendocrine and immunological functions that

influence mortality (e.g. dysregulation of the hypothalamic-pituitary-adrenal axis).

Second, depression may impact patients' ability to adhere to screening measures, cancer

treatments or behaviours that maintain health (69). Third, a number of the symptoms of

cancer and the side effects of its treatment are similar to those of depression, including

increased sleep and appetite disturbance, fatigue and concentration difficulties.

Therefore, measurement issues and symptom overlap may lead to side effects being

misdiagnosed as depression.

The most discernible effect of comorbid depressive symptoms and cancer is on QoL.

Depressive symptoms have been found to affect global QoL scores in HNC patients

during and after treatment (67). For example, Verdonck-de Leeuw et al. (68) reported

that patients with a high level of psychological distress (as measured by the Hospital

Anxiety and Depression Scale; HADS) (69), had significantly worse scores regarding

QoL on a global HRQoL scale, in a sample of 58 HNC patients undergoing curative

treatment. These findings provide cause for further investigation into clarifying the rates of and designing interventions for depression in HNC.

Best practice clinical guidelines

The etiology and relationship between health behaviour and affect risk factors and treatment outcomes in HNC is complex. Due to the evidence for the potential negative effects of continued smoking, alcohol misuse and psychological distress such as depression, numerous evidence based clinical guidelines for cancer patients overall (52, 69, 71), as well as specifically for HNC (52, 72), make recommendations for best practice including screening and brief advice or referral for appropriate further assessment and support. Despite the existence of best practice guidelines, translation of their evidence based recommendations is inconsistent overall (73, 74). Within oncology, evidence suggests that assessment and intervention provided by health professionals for tobacco use (40, 75-77), psychological distress (55, 78-81) and alcohol misuse and other health risk behaviours (82, 83) is suboptimal.

Tobacco

Numerous national and international organisations and best practice guidelines recommend that clinicians identify tobacco use status, and advise patients on the benefits of quitting (69, 84-86). The US Department of Health and Human Services Public Health Service developed an evidence based cessation intervention model known as the "5 As": (i) Ask about tobacco use at every clinic visit, (ii) Advise to quit, (iii) Assess interest in quitting, (iv) Assist by providing counselling and pharmacotherapy, and (v) Arrange follow-up (69). The Public Health Service *Treating Tobacco Use and Dependency* tobacco treatment guidelines are endorsed by key oncology professional societies, including the American Association for Cancer Research (87) and the

American Society of Clinical Oncology (88). The National Cancer Network *Smoking Cessation Clinical Practice Guidelines* recommend standardised initial and periodic follow-up assessment according to smoking status and all cancer patients who are current smokers receive evidence based cessation treatment including pharmacotherapy and behavioural counselling, and follow-up (89).

Despite recognition of the efficacy and importance of such guidelines, evidence indicates that they have been poorly implemented in oncology settings (90-92). Only 38% of surveyed National Cancer Institute Cancer Centres record smoking as a vital sign (92). A survey of individual oncologists in a wide variety of treatment settings indicated that approximately 61% reported providing smoking cessation services (93). In a survey of nurses, 73% self-reported providing some level of cessation interventions. However, questions about each of the 5 As suggested suboptimal provision of care according to Public Health Service guidelines (94).

Barriers to executing evidence based smoking cessation strategies include lack of resources, lack of institutional incentives, and poor provider awareness and education (95). A recent study of 1500 physicians evaluated practices, perceptions, and barriers to tobacco assessment and cessation in cancer patients (96). Although more than 90% of respondents endorsed that smoking cessation should be a standard part of cancer care, only 40% reported discussing medications or providing active cessation support. The dominant barriers to optimal provision of care were education, perceived inability to get patients to quit and patient resistance to cessation interventions.

Most research into clinician provision of smoking cessation care for cancer patients has been conducted across heterogeneous cancer types. However, the literature suggests that the provision of this care is suboptimal for HNC patients also (97). In a 2011 study, 65% of current smokers receiving treatment for lung or HNC reported that they were offered smoking cessation assistance by a medical professional (98).

Alcohol

Due to the evidence for the carcinogenic nature of alcohol, numerous guidelines exist that recommend limiting alcohol consumption to reduce cancer risk in the general population (99, 100). The Cancer Council Australia's Position Statement on Alcohol and Cancer Risk recommends that to reduce their risk of cancer, people limit their consumption of alcohol (101). The American Cancer Society advises that for those already diagnosed with cancer, alcohol intake could affect the risk of developing a new cancer (102). The Society also advises there are some cases during cancer treatment in which alcohol should be avoided. In a clinical review of HNC, the authors state that stopping smoking and drinking less alcohol is the most effective way to reduce mortality (103). However, despite the recognition that continued drinking combined with smoking increases risk of mortality in HNC, there are no current clinical guidelines that make recommendations for clinicians to assess and advise HNC patients to stop drinking alcohol during treatment.

Given the lack of guidance for clinicians in regard to recommendations for alcohol use during HNC treatment, it is not surprising that data on clinicians' provision of this care in HNC is non-existent. It has been reported that screening and brief intervention for risky alcohol use in cancer settings is poorly implemented (104) and consequently substance misuse including alcohol misuse is frequently underdiagnosed among cancer

patients (105). A retrospective chart review of two outpatient cancer clinics in the US found that oncology practitioners poorly and inconsistently performed assessment for alcohol consumption among young adult cancer survivors (106). In addition to the lack of specific guidelines in this area, other barriers to clinician assessment and intervention for alcohol use in cancer generally, and particularly in HNC, may include stigmatisation of addictive behaviours and lack of education about the health risk consequences of harmful alcohol use (104).

Depression

Professional associations and best practice guidelines (107-111) including the NCCN *Clinical Practice Guidelines in Oncology: Distress Management* (52) recommend that those responsible for the care of cancer patients routinely screen for distress and, as appropriate, refer for further assessment and support. Despite evidence based guideline recommendations, screening and referral of cancer patients for distress is not routinely conducted by clinicians responsible for the clinical management of cancer (52, 55, 112). Beginning in 2015, the American College of Surgeons Commission on Cancer has required cancer centres to implement programs for distress screening as a criterion for accreditation (111). A recent cross-sectional survey of 20 NCCN Institutions reported only 60% of services conducted outpatient distress screening, and even fewer services reported screening all patients (30%) as outlined in the NCCN standards (113).

Due to the over representation of mental illness, particularly depression in HNC patients, recently developed Australian dietetic guidelines specific to HNC patients recommend screening for distress by oncology dietitians (114). However, whilst information on distress referral rates in HNC patients is severely lacking, it has been suggested that distress is especially overlooked in this population (68, 115). Barriers to

effective distress screening and referral for cancer patients include disagreement between members of an oncology treatment team around who should perform screening, lack of knowledge about psychosocial care, lack of information about appropriate referral sources, confusion about how and when to make a referral and resource and staffing concerns (80, 81). Consequently, formal distress screening and policies for referral are recommended by best practice guidelines to ensure a consistent level of care is provided.

Research aims

The overall aim of this thesis is to identify and address important gaps in the evidence base regarding modifiable behavioural and affect risk factors among a disadvantaged group; the HNC population. This includes an evaluation of strategies to improve the provision of care for patients with HNC undergoing RT. The intention is to recognise, describe and address the complexity of the etiology and management of these malignancies. This thesis does not represent a chronological program of research but describes a related body of work with independent research questions. This research took significant steps towards a robust approach to HNC care that acknowledges the need for recognition of risk and recurrence factors and evidence based best practice care when it comes to the management of HNC patients. This approach necessitated literature reviews, observational and experimental studies and is presented in six papers which form the basis of this thesis.

Specifically, this dissertation aimed to:

1. Describe the rates and co-occurrence of tobacco smoking, alcohol use and depressive symptoms in a sample of HNC patients undergoing RT (Paper One);

2. Systematically review the literature to determine the impact of interventions to improve clinician provision of screening and appropriate referral of patients with cancer for distress (Paper Two and Paper Three);

3. Assess the effectiveness of clinical practice change strategies in improving dietitian implementation of best practice guideline recommendations for HNC patients (Paper Four and Paper Five); and

4. Systematically review the literature to examine the effectiveness of smoking cessation interventions on smoking cessation rates in adult HNC patients (Paper Six).

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SMOKING, DRINKING AND DEPRESSION: COMORBIDITY IN HEAD AND NECK CANCER PATIENTS UNDERGOING RADIOTHERAPY

PAPER ONE

INTRODUCTION TO PAPER ONE

Whilst it has been acknowledged that a number of factors contribute to the etiology, treatment outcomes and risk of recurrence in HNC, specifically, tobacco smoking (1-4), alcohol use (1, 5-8) and depression (1, 9-13), the evidence base on rates and patterns of these factors is limited. Wide ranging estimates exist due in part to varying definitions and measures, heterogeneous groups (all cancer sites and stages of treatment) and a lack of current studies. Specifically, data is lacking on current estimates for tobacco smoking, alcohol use and depressive symptoms in the Australian HNC population. Furthermore, even less focus has been given to determine the co-occurrence of these factors in this cancer population, despite the recognition that these often cluster together in other populations (14-16).

Consequently, Paper One aimed to describe the rates and co-occurrence of tobacco smoking, alcohol use and depressive symptoms in a recent Australian sample of HNC patients undergoing RT. In doing so, this paper characterised the population that this thesis focused on. In order to design effective evidence based interventions for HNC patients, we must first recognise the complex relationship between behavioural and affect risk factors, their continued occurrence and co-occurrence throughout treatment and endeavour to address them as part of HNC patient care.

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PAPER ONE: SMOKING, DRINKING AND DEPRESSION: COMORBIDITY IN HEAD AND NECK CANCER PATIENTS UNDERGOING RADIOTHERAPY

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Associated Appendices:

Appendix   A1 Ethics approval for Eating As Treatment trial
A2 Information and consent form for Eating As Treatment trial
A3 Study assessment measures for Eating As Treatment trial

Abstract

Objective: Despite negative impacts of tobacco smoking, alcohol consumption and depressive symptoms on treatment outcomes among HNC patients, little research has been conducted investigating their co-occurrence in this group. We aimed to determine the prevalence of smoking; alcohol consumption; depressive symptoms; and their co-occurrence in a sample of HNC patients undergoing RT.

Method: 307 HNC patients agreed to participate in a multi-site stepped-wedge RCT evaluating the effectiveness of a dietitian-delivered health behaviour intervention to reduce malnutrition in patients with HNC undergoing RT. During week one of RT patients completed measures of smoking (carbon monoxide; CO), alcohol consumption (Alcohol Use Disorders Identification Test; AUDIT) and level of depression (Patient Health Questionnaire-9; PHQ-9).

Results: Approximately one-fifth (21%) of patients had two or more co-occurring problems: current smoking, hazardous alcohol use and/or likely presence of a major depressive episode (MDE). Approximately one-third (34%) of the sample were current smokers, one-third (31%) were drinking hazardously and almost one fifth (19%) had likely cases of depression.

Conclusion: Comorbidity of smoking, hazardous alcohol use and MDE is high in HNC patients and interventions need to address this cluster of cancer risk factors.

Introduction

Tobacco smoking, alcohol consumption and depressive symptoms are important determinants and highly prevalent factors in the onset, prognosis and recovery from HNC. Continued smoking in cancer patients has been associated with several adverse outcomes: an increased risk for other smoking related diseases, second primary tumours, disease recurrence, poorer response to RT, decreased survival, decreased QoL scores and increased toxicity and side effects from RT (1-6). In addition to the increased risk for developing second primary tumours, poor RT treatment outcomes in HNC patients who continue smoking during treatment can be explained by a reduced tumour oxygen supply caused by the increase in carboxyhemoglobin in smokers (7). Continued alcohol intake at problematic levels has been associated with secondary cancers, decreased survival rates (8-10) and lower QoL scores (5) in HNC patients. There is robust evidence that for cancers of the mouth, pharynx, larynx and oesophagus, DNA damage is attributable to acetaldehyde, the carcinogenic metabolite of ethanol oxidation (11, 12). Depression in cancer patients is associated with increased morbidity and possibly increased mortality (13, 14). In HNC specifically, depressive symptoms have been associated with poorer QoL scores (15) and found to be predictive of malnutrition during treatment (16). Relationships between psychosocial factors and cancer progression have been observed and data from patients with existing tumours show that those who tend toward depressive coping methods such as hopelessness might experience accelerated disease progression (17).

Given the importance of these risks factors, a number of studies have described patterns of tobacco or alcohol use, or depressive symptoms among HNC patients undergoing treatment. Prevalence estimates of these risk factors vary considerably. For example,

evidence from observational and intervention studies report between one third and 75% of HNC patients continue to smoke after diagnosis (3, 18-22). Despite the varying rates, even the lowest estimates are much higher than for the general population (23). Between 37-54% of HNC patients continue to consume alcohol after diagnosis, with up to 16% continuing to drink at a hazardous level (18, 24). Estimates of the prevalence of depression in HNC patients range from 15% to 57% (15, 18, 25-28). Variability in the reported consumption of alcohol and tobacco use among HNC patients, and the prevalence of depression in this group may be attributable to differences in the underlying prevalence rates in the population where the studies were conducted, period effects, or differences in measurement of tobacco (29) or alcohol use, (9, 18, 24) or differences in diagnostic measurements for depression (30).

Of particular concern for both the immediate clinical outcomes of HNC patients, and their longer-term health is the co-occurrence of these risk factors. The presence of multiple health risk factors markedly increases the likelihood of adverse treatment outcomes. Smoking, alcohol misuse and depressive symptoms tend to cluster and their relationship is complex (31). The combination of smoking and alcohol use is common and patients may drink alcohol or smoke in an attempt to "self-medicate" depressive symptoms (32). Also, depression is associated with cravings for alcohol and nicotine (33). Furthermore, it has been suggested there is a causal link between alcohol misuse and increased likelihood of depression (34).

Despite the high rates of smoking, alcohol consumption and depression reported in HNC patients and their effect on patient outcomes, there is little research investigating the rates of comorbidity of these factors in HNC patients. Duffy et al. (5, 25) conducted

a cross-sectional study, and a subsequent cohort study to examine the prevalence and associations between smoking, problem drinking, depressive symptoms and QoL among HNC patients recruited from a proportion of a sample of patients from Veterans Affairs hospitals in the US, which included patients at varying stages of treatment. In the cross-sectional study of 80 HNC patients, 76% scored positive for one or more of smoking, at-risk alcohol intake and significant depressive symptoms. The follow-up cohort study with a convenience sample of 973 HNC patients at varying stages of treatment reported similar results. However, the authors did not specify the prevalence of those patients with two or more of these issues.

Given the clinical and public health salience of tobacco smoking, alcohol consumption and depressive symptoms among HNC patients, and the limitations of previous studies, a more comprehensive assessment of risk factors, and their co-occurrence among HNC patients is required. Such information is important for health service planning and to ensure that care is provided to HNC patients that maximises the likelihood of a positive long term prognosis. In particular, identification of those HNC patients who have co-occurrence of smoking, alcohol consumption and depressive symptoms before undergoing radiation treatment, may assist in considering interventions in addition to RT.

This is the first study to examine: smoking status; alcohol consumption; the severity of depressive symptoms; and their co-occurrence assessed during the first week of RT. Our primary objectives were to:

i) Report the rates and severity of tobacco smoking, alcohol consumption, depressive symptom severity and likelihood of MDE; and

ii) Describe the pattern of co-occurrence of these factors

Materials and methods

Procedures

In this cross-sectional study, 307 patients participated in a multi-site stepped-wedge RCT (Trial registration no. ACTRN12613000320752) and completed baseline assessments. The trial evaluated the effectiveness of a dietitian-delivered health behaviour intervention to reduce malnutrition in patients with HNC undergoing RT (30). Sites participating in the RCT generated a list of patients who met eligibility criteria using treatment planning software, multi-disciplinary team meetings and/or clinician referrals. Eligible patients were approached with information about the study (by their radiation oncologist and/or an independent research officer). After an opportunity to consider the information and have any questions answered, for patients who remained interested, eligibility criteria were confirmed and written informed consent taken (Appendix A2).

Inclusion criteria

Patients eligible for inclusion in the trial met the following criteria:

- Aged 18 years or older

- Pathologically confirmed diagnosis of HNC, involving the nasopharynx, oropharynx, oral cavity, larynx, or hypopharynx, requiring definitive or postoperative RT with curative intent (chemoradiation including neoadjuvant and adjuvant chemotherapy were permitted)

- Receiving RT to a dose of at least 60Gy with regional nodal irradiation including as a minimum ipsilateral nodal levels II-III

- Available for follow-up for at least six months post study initiation

- Capacity to provide written informed consent

Exclusion criteria

- Inability to communicate in English

- Presence of organic brain diseases (impairing ability to complete questionnaires satisfactorily)

- Likely insignificant oral or pharyngeal mucositis as a complication of RT treatment (patients with T1/T2 glottic carcinoma undergoing small-field RT or T1/T2 tonsil cancer undergoing unilateral treatment were excluded)

The study received approval from the Human Research Ethics Committee (HREC) of Hunter New England Health (HREC/12/HNE/108; HNEHREC: 12/04/18/4.06) (Appendix A1).

Measures

Across five sites, during the first week of RT, an independent research officer administered assessment instruments (Appendix A3). These included demographic information, patient clinical characteristics, measures of smoking and alcohol consumption and related features (level of nicotine dependence, intentions to change smoking or alcohol consumption) and level of depression. The research officer also conducted chart reviews to extract cancer diagnosis, staging and treatment data.

Demographic characteristics

Demographic information included age (years), gender (male/female), marital status, Aboriginal and Torres Strait Islander (ATSI) status, education, accommodation and employment status.

Clinical characteristics

Clinical information included tumour site, tumour stage, proposed RT dose, proposed chemotherapy, surgery and feeding tube status (prophylactic percutaneous endoscopic gastrostomy; PEG or nasogastric tube; NGT).

Smoking

Patients were asked about their smoking behaviour (ever smoked, current smoker, most recent cigarette, number of cigarettes within the last 24 hours, current nicotine replacement therapy; NRT use). Expired CO provided biochemical verification of smoking status. The Micro 11 Smokerlyser assessed breath levels of CO for all patients. A cutoff of ≥ 4 CO parts per million (PPM) was used to classify abstinence from smoking, as has been suggested to increase specificity in determining smoking abstinence, particularly for those patient groups that might be more inclined to misrepresent their smoking status as has been found in HNC patients (35-41). Nicotine dependence was measured via the Fagerstrom Test for Nicotine Dependence (FTND) - a six-item, reliable and valid self-report questionnaire designed to assess the strength of nicotine dependence (42). Item scores are summed to produce a total score, with higher scores indicating higher levels of nicotine dependence (0–2=very low; 3–4=low; 5=medium; 6–7=high; 8–10=very high dependence).

As a descriptive measure of chronicity and severity of smoking, intention to change was assessed using an adapted version of the measure developed by Etter et al. (43). For smoking, participants were asked to indicate the statement that best reflected their current plan to quit smoking; *I am not thinking about quitting in the near future, I intend to quit in the next 6 months, I intend to quit in the next 30 days, I have quit in the last 6 months, I have quit for 6 months or more,* or *Not applicable – Never smoked.*

Alcohol consumption

The AUDIT (44) is a ten item self-report measure developed by the World Health Organisation (WHO) to identify harmful patterns of alcohol use over the preceding 12 months (including harmful use, hazardous use and dependence). Items are summed to produce a total score, with scores ≥ 8 indicating harmful or hazardous alcohol use, as well as possible alcohol dependence. The AUDIT-Consumption (44) consists of the first three items of the AUDIT (frequency of use, typical consumption and frequency of six or more standard drinks), and provides an index of alcohol use. It is a reliable indicator of heavy drinking and also demonstrates adequate sensitivity and specificity for detecting active alcohol abuse and dependence (44). It was employed to detect changes in quantity and/or type of alcohol consumed more recent to the start of treatment and referred to alcohol use in the preceding two months. A score of ≥ 4 in men and a score $\geq$ 3 or more in women is considered positive for identifying hazardous drinking.

As a descriptive measure of chronicity and severity, intention to change was assessed. Participants were asked to indicate the statement that best reflected their current plan to cut down on drinking; *I am not thinking about cutting down in the near future, I intend to cut down in the next 6 months, I intend to cut down in the next 30 days, I have cut down in the last 6 months,* or *I have cut down for 6 months or more.* This was measured even in those who reported never having a drink in the last two months, as the statements included options for having cut down.

Depression

The PHQ-9 (45) is a self-administered nine-item questionnaire that can either be scored continuously to assess depressive symptoms (depressive severity), or scored categorically to assess the likely presence of MDE. Participants are asked to rate (on a

scale of 0–3) the frequency of various MDE criteria over the previous two weeks. A cutoff score of ≥ 8 has been suggested for identifying MDE in cancer patients (45), and the severity of the depression can be rated as 0-4 = minimal; 5-9 = mild; 10-14 = moderate; 15-19 = moderately severe; 20-27 = severe.

Statistical analysis

Descriptive statistics (means, standard deviation; SD and frequencies) were conducted on all demographic and health variables, smoking, nicotine dependence, alcohol consumption and depressive symptoms. Crosstab analyses were conducted to examine the co-occurrence of current smoking (≥4 CO PPM), hazardous alcohol use (AUDIT-C score ≥3 for women, ≥4 for men) and likely presence of MDE (PHQ-9 score ≥8). For the subset of participants with complete comorbidity data (N = 276), agglomerative hierarchical cluster analysis was utilised to investigate the relationship between continuously measured smoking (CO PMM), alcohol (AUDIT-C) and depression (PHQ-9) comorbidities and patient demographics (age and gender). A dissimilarity matrix was first estimated using the 'gower' metric, which is appropriate for mixed variable types (46). Clustering was subsequently performed on this matrix using the 'agnes' function of the 'cluster' package in R (48). The optimal clustering structure was determined via examination of the dendrogram, face validity and interpretability of the clusters, and parsimony.

Results

Patient characteristics

The sample is described in Table 1. The mean age was 58 (*SD* 10) and most were male. 31% were separated, divorced or never married. Just over half (56%) had cancer of the oropharynx and most had stage IV (65%) cancer. All patients were scheduled to

undergo RT; about a third had surgery prior to RT. Almost a quarter (23%) had a PEG

feeding tube prior to starting RT and only 2% had a NGT.

Smoking, alcohol and depression

Baseline smoking, alcohol consumption and depressive symptoms are presented in

Table 2.

Comorbidity

Of 276 patients with complete data for all three outcomes, 21% scored positive for two

or more of the following problems: current smoking ($\geq$4 CO PPM), hazardous alcohol

use (AUDIT-C score $\geq$3 for women, $\geq$4 for men) and likely presence of MDE (PHQ-9

score $\geq$8) (Figure 1). For those patients who had ever smoked and reported reducing

their alcohol intake (from four or more times per week in the 12 months before baseline

to less than that in the two months before baseline), 32% (*n*=13/41) also reported

quitting smoking recently (i.e. their last cigarette was between two weeks and six

months prior to baseline). Due to the subjective nature of hierarchical clustering, there

are no fit statistics or threshold available with which to choose an 'optimal' number of

clusters. The final model, therefore becomes a trade-off between the number of clusters

and the within cluster variability; visually inspecting the dendrogram, a seven cluster

solution appeared to be a satisfactory tradeoff. Table 3 contains the mean (SD) and

frequencies (%) of the variables within each cluster in the chosen model.

Although seven potential clusters were identified, after examining the cluster sizes it

was evident that the bulk of the participants (N = 272) were described by four of the

clusters. The remaining four participants in the final three clusters could be considered

'outliers'. Cluster 1 was the largest cluster (N = 142), was entirely male, with mean

Table 1. Patient characteristics of HNC patients at week one of RT ($N = 307$)

Variable	N/Mean	%/SD
Age (years)	58	10.4
Sex		
Male	244	80%
Female	63	21%
Country		
Australia	198	65%
UK & Ireland	38	12%
Other	71	23%
Primary language		
English	285	93%
Other	22	7%
ATSI		
Yes	6	2%
No	300	98%
Marital status		
Married	156	51%
De-facto/common law couples	37	12%
Widowed	12	4%
Separated/divorced	57	18%
Single, never married	40	13%
Other	5	2%
Education level		
4 years of high school or less	112	36%
6 years of high school	155	50%
University/Vocational College	146	48%
Other	1	<1%
Accommodation (past year)		
Private residence (own home, private rental)	297	97%
Partially supported living (Department of housing, independent unit in retirement village/nursing home)	9	3%
Other	1	<1%
Employment (past year)		
No job	19	6%

Full time	152	50%
Part time/casual	31	10%
Housework/stay at home parent	7	2%
Studying	2	1%
Retired/volunteer	84	27%
Other	12	4%
Tumour site		
Nasopharynx	23	8%
Oropharynx	171	56%
Oral Cavity	66	22%
Larynx	29	9%
Hypopharynx	11	4%
Unknown Primary	7	2%
Tumour stage		
I	12	4%
II	39	13%
III	57	19%
IV	199	65%
RT	307	100%
Surgery prior to RT	97	32%
Concurrent chemotherapy	247	81%
Prophylactic PEG	71	23%
Prophylactic NGT	7	2%
Hospital site		
Site 1	23	8%
Site 2	100	33%
Site 3	83	27%
Site 4	101	33%

Table 2. Smoking, alcohol consumption and depressive symptoms at baseline

Variable	N (%)
Smoking	
Current smoker (self-report) (*n*=304)	40 (13%)
Number of cigarettes within last 24 hours (*n*=38)	
0-9	28 (74%)
10-20	9 (24%)
21-30	1 (3%)
Ever smoked (*n*=305)	232 (76%)
Currently using NRT (*n*=232)	18 (9%)
Most recent cigarette (*n*=230)	
<24hours	38 (17%)
<2 weeks	11 (5%)
<1 month	11 (5%)
<6months	46 (20%)
<1 year	9 (4%)
<5 years	16 (7%)
>5 years	99 (43%)
Nicotine Dependence; FTND (patients who had smoked in the last month) (*n*=53)	
Very low	19 (36%)
Low	19 (36%)
Medium	6 (11%)
High	9 (17%)
Very high	0
CO confirmed current smokers (*n*=280)	
CO PPM ≥4	94 (34%)
Intentions to change (smoking) (*n*=295)	
I am not thinking about quitting in the near future	15 (5%)
I intend to quit in the next 6 months	15 (5%)
I intend to quit in the next 30 days	16 (5%)
I have quit in the last 6 months	67 (23%)
I have quit for 6 months or more	113 (38%)
Not applicable – Never smoked	71 (24%)
Alcohol consumption	
AUDIT (past year)	
Frequency of use (how often do you have a drink containing alcohol?) (*n*=303)	
Never	46 (15%)

Monthly or less	56 (19%)
2 to 4 times a month	34 (11%)
2 to 3 times a week	57 (19%)
4 or more times a week	109 (36%)

Typical consumption (alcohol drinks on a typical day when drinking?) *(n=257)*

1-2	129 (50%)
3-4	66 (26%)
5-6	43 (17%)
7-9	5 (2%)
10 or more	14 (5%)

Frequency of 6 or more standard drinks on one occasion (*n*=257)

Never	111 (43%)
Less than monthly	54 (21%)
Monthly	40 (16%)
Weekly	30 (12%)
Daily or almost daily	22 (9%)
Harmful/hazardous use (AUDIT ≥8) (*n*=294)	77 (30%)

AUDIT-C (past 2 months)

Frequency of use (how often do you have a drink containing alcohol?) (*n*=306)

Never	114 (37%)
Monthly or less	47 (15%)
2 to 4 times a month	38 (12%)
2 to 3 times a week	47 (15%)
4 or more times a week	60 (20%)

Typical consumption (alcohol drinks on a typical day when drinking?) *(n=192)*

1-2	119 (62%)
3-4	39 (20%)
5-6	23 (12%)
7-9	2 (1%)
10 or more	9 (5%)

Frequency of 6 or more standard drinks on one occasion (*n*=192)

Never	133 (70%)
Less than monthly	18 (9%)
Monthly	14 (7%)
Weekly	14 (7%)

Daily or almost daily	13 (7%)
Hazardous drinking (AUDIT-C ≥3 for women, ≥4 for men) (*n*=306)	94 (31%)
Intentions to change (alcohol use) (*n*=301)	
I am not thinking about cutting down in the near future	140 (47%)
I intend to cut down in the next 6 months	7 (2%)
I intend to cut down in the next 30 days	14 (5%)
I have cut down in the last 6 months	105 (35%)
I have cut down for 6 months or more	35 (12%)
Depressive symptoms (PHQ-9) (*n*=303)	
Minimal	197 (65%)
Mild	70 (23%)
Moderate	22 (7%)
Moderately severe	11 (4%)
Severe	3 (1%)
Likely presence of MDE (PHQ-9 score≥8)	58 (19%)
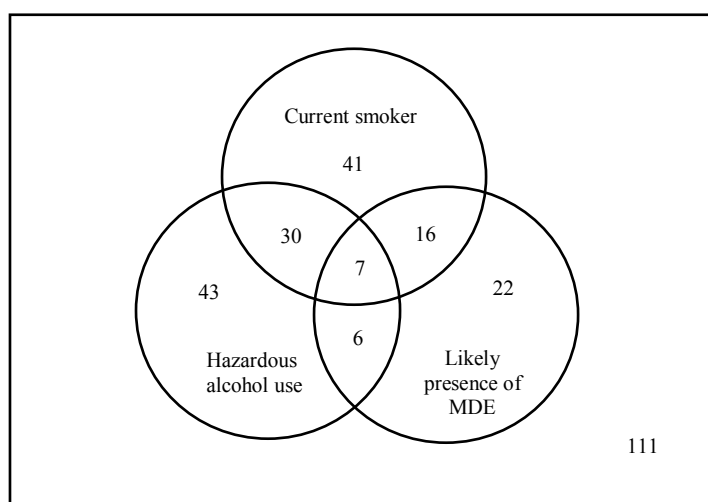
Figure 1. Comorbidity at baseline

Table 3. Cluster characteristics

Cluster (N)	Alcohol (Mean(SD))	Smoking (Mean(SD))	Depression (Mean(SD))	Age (Mean(SD))	Males (N(%))	Females (N(%))
Cluster 1 (N = 142)	1.5 (1.5)	3.0 (1.3)	2.7 (2.5)	58.9 (8.8)	142 (100%)	
Cluster 2 (N = 49)	2.2 (1.5)	2.7 (2.1)	3.9)3.4)	56.2 (13.1)		49 (100%)
Cluster 3 (N = 33)	1.5 (1.9)	5.5 (4.3)	12.2 (5.6)	56.1 (12.1)	33 (100%)	
Cluster 4 (N = 48)	7.8 (2.2)	5.1 (3.3)	2.9 (2.4)	58.6 (9.7)	48 (100%)	
Cluster 5 (N = 1)	8.0 (.)	3.0 (.)	6.0 (.)	72.0 (.)		1 (100%)
Cluster 6 (N = 2)	0.0 (0.0)	17.5 (4.9)	6.0 (7.1)	54.5 (2.1)		2 (100%)
Cluster 7 (N = 1)	5.0 (.)	21.0 (.)	16.0 (.)	60.0 (.)	1 (100%)	

comorbidity scores below the thresholds indicative of hazardous drinking, smoking or depression. Cluster 2 (N = 49) was similar to Cluster 1, except that it contained all females. Cluster 3 (N = 33) participants were male, and the mean comorbidity scores were indicative of smoking and depression, but not of hazardous alcohol consumption. Cluster 4 (N = 48) was also entirely male, and the mean comorbidity scores were indicative of hazardous drinking and smoking, but not of depression. However, it must be noted that the SDs for each of the means are quite large, and therefore confidence

intervals would overlap between clusters. Of the remaining 'outlier clusters', Cluster 5 contained a single female participant, with hazardous drinking levels, low CO PPM and mild depression. Cluster 6 contained two females, with zero alcohol consumption, heavy smoking, and mild depression. Cluster 7 contained a single man, with hazardous drinking, heavy smoking, and high depression.

Discussion

Comorbidity

This is the first study to examine: smoking status; alcohol consumption; the severity of depressive symptoms; and their co-occurrence in HNC patients assessed during the first week of RT. Approximately one fifth of the sample ($n = 59/276$; 21%) scored positive for two or more problems; smoking, hazardous alcohol consumption and probable depression. Interestingly, of patients who reported i) having smoked in their lifetime; and ii) reducing their alcohol intake prior to baseline, approximately one third reported quitting smoking relatively recently. This is in line with previous research that suggests smoking cessation can enhance sobriety from alcohol, as opposed to impede alcohol abstinence (49).

Four main clusters were identified, corresponding to males and females without any comorbid substance use and depression, males with comorbid smoking and depression, and males with comorbid smoking and drinking. These clusters suggest that: i) males may be more likely to exhibit comorbid conditions, and that, ii) if comorbid conditions are present, smoking may be accompanied by either depression or problematic drinking. This fits with previously reported increased rates of smoking (50) or drinking (51) alone in male HNC patients. There is considerable debate in the literature about the extent and

nature of gender differences in the psychosocial adaptation to cancer (52). However, our findings offer a further insight into a group of male HNC patients that may require additional supports due to co-occurring issues.

In an oncology setting, HNC patients may feel overwhelmed by recent diagnosis, treatment schedules and side effects. Health professionals' focus may be primarily on treating the malignancy and resources and time are limited. In such circumstances, it would be valuable to treat comorbid problems together rather than separately. Treatments such as cognitive behaviour therapy (CBT) and motivational interviewing (MI) can be employed for smoking, problematic alcohol consumption and depression, and evidence suggests that integrated treatment for comorbid problems is effective (53-55).

There is little research investigating effective interventions for such comorbidity in this population. The co-occurrence of reduced alcohol intake and smoking in our participants prior to baseline, demonstrates the potential for concurrent reductions in smoking and alcohol use in the HNC population. For those HNC patients who continue to smoke, drink alcohol at hazardous levels or experience depressive symptoms during treatment and particularly those with co-occurrence of these issues, a multicomponent, intensive treatment may be beneficial (18).

Smoking

Consistent with previous research, approximately one third (34%) of the sample were current smokers (3, 18, 21, 22). Continued smoking throughout cancer treatment has negative implications for treatment efficacy and survival (1-6). However, a substantial proportion of patients in our study were smoking at the beginning of RT. Coupled with

the potential for those who had recently quit to relapse over the course of treatment, assessment of smoking status and the development of cessation interventions in this group warrants attention. A recent review (56) found that very few smoking cessation trials have been conducted with the HNC population but that a multicomponent approach (i.e. pharmacotherapy and evidence based psychosocial therapies) may be beneficial, also addressing co-occurring risk factors.

Self-reported smoking status was also much lower than reported in previous studies with HNC patients (3, 18, 21, 22). Given the research that suggests patients may minimise their smoking status, particularly in smoking related cancers, it may be that some patients misrepresent their smoking status (39). There is evidence that for some cancer patients, particularly those with smoking related cancers such as HNC, diagnosis is sufficient to produce abstinence (19, 57-59). However, there is also a considerable rate of relapse for HNC patients who quit smoking; as high as between 13 and 90% depending on follow-up period (21, 38, 60, 61). Given the evidence that demonstrates the negative effects of tobacco use on treatment outcomes and survival, smoking status should be measured and biochemically confirmed at diagnosis, throughout treatment and at follow-up in this population (62), with a view to offering assistance with smoking cessation interventions.

Alcohol consumption

Compared to smoking, less research has been conducted on alcohol consumption in HNC patients and the results of our study help to characterise this health behaviour in this cancer population. The rate of alcohol consumption (last 12 months 85%; last two months 63%) in our sample was comparable to that of current drinkers (75%) in a sample ($n = 107$) of newly diagnosed HNC patients (63). Further, about one third of our

sample scored positive for hazardous drinking, relative to the past two months (AUDIT-C). This finding combined with those who were found to be at risk of alcohol related disorders (30%; AUDIT; past 12 months) is similar to rates described in previous studies (5, 24, 64). Given the association between problem drinking and secondary cancers, decreased survival rates and poorer QoL (5, 8-10), this degree of problem drinking in HNC patients is concerning.

It has been suggested that the high rate of continued drinking in this population may be in part explained by lack of patient awareness of the association between alcohol and HNC (24). Indeed, almost half of our sample endorsed "I am not thinking about cutting down (alcohol use) in the near future". Health care personnel across numerous specialties have reported that they do not deem discussing alcohol acceptable (64). However, physicians involved in the treatment of HNC patients are well placed to provide information about the hazards of continued drinking and studies of primary care patients have demonstrated that most are open to advice from physicians about their alcohol use (65). Opportunities also exist for nurses and other health care professionals to routinely ask about alcohol use to hospital inpatients (66). This opportunity for intervention is especially important in HNC patients where alcohol consumption in combination with smoking is responsible for the majority of these cancers (67) and continued use increases the risk of a secondary cancer (10). A recent study found an alcohol abstinence program for surgically treated HNC patients was effective in reducing morbidity and improved outcomes, including significantly reduced hospital stay and time lapse to starting adjuvant RT in the contracted group (68).

Despite the high rate of current drinking at baseline, a proportion of patients had cut down on drinking four or more times per week from 36% in the last 12 months to 20% in the last two months. More patients were also drinking in the lower range of drinking on a typical day in the past two months as compared to the past 12 months. It may be that as for smoking, the symptoms or diagnosis of cancer is sufficient to change alcohol use for some, whilst others who continue to drink at harmful levels despite a cancer diagnosis need additional support to cut down.

Depression

Almost one fifth (19%) of our patients were identified as having likely cases of depression using the PHQ-9. This is consistent with the lower range of rates reported in the HNC literature (15, 18, 24-27). Identifying the prevalence of depression in HNC patients is complicated by the use of varying screening and diagnostic tools, unclear reporting of depression diagnoses versus depressive symptoms and time of measurement (e.g. pre or post cancer treatment). However, even conservative estimates of depressive symptoms and likely cases of depression in this cancer population at the pretreatment stage warrants attention. The importance of screening for depression and offering referral for psychosocial support has been highlighted in the numerous evidence based cancer guidelines that recommend this delivery of care (69-71).

Limitations

A limitation of the study is that, although a valid self-report tool was used to measure the likelihood of meeting criteria for a major depressive disorder, this was not confirmed by a diagnostic assessment and may have resulted in an overestimation of patients with depression. The patients in our sample were undergoing treatment with curative intent. Consequently, our findings are limited to this population. Rates of health behaviours such as smoking and alcohol use as well as depression may vary in

HNC populations that are undergoing supportive care or no treatment at all. The results from the cluster analysis are descriptive only, and the large standard errors for the mean estimates indicate that the comorbidities scores are not significantly different between the clusters.

Conclusions

The occurrence of smoking, alcohol consumption, and depressive symptoms was considerable. For a sizeable group of patients, these problems were co-occurring. Screening and assessment of these behaviours and conditions should be conducted prior to treatment in order to provide intervention for those who continue to smoke or for recent quitters, consume alcohol or experience depression. Additional support may be necessary for a subgroup with comorbid issues. Treating smoking, hazardous alcohol use and/or depressive symptoms is likely to be associated with improved treatment outcomes and greater survival in HNC patients.

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SCREENING AND APPROPRIATE REFERRAL OF PATIENTS WITH CANCER FOR DISTRESS

PAPERS TWO & THREE

INTRODUCTION TO PAPER TWO AND PAPER THREE

Paper One added to the evidence base by presenting the rates and co-occurrence of tobacco smoking, alcohol use and depressive symptoms in a recent Australian sample of HNC patients undergoing RT. Whilst all three of these factors are key to HNC care, distress is now internationally endorsed as the sixth vital sign in cancer (1), screening for distress is a requirement for some cancer centres' accreditation (2, 3) and is included in numerous best practice guidelines for cancer (2, 4-8). Consequently, Paper Two and Paper Three focused on the existing literature regarding the translation of this evidence into cancer care.

The research presented in Paper Two and Paper Three was designed to critically review existing studies of interventions that aimed to improve clinician provision of screening and appropriate referral of patients with cancer for distress. This review aimed to synthesise the available literature in an effort to identify effective strategies as well as areas for improvement for implementation of distress screening and referral. Specific to this thesis body of work, the review informed the development of practice change strategies employed in the RCT presented in Paper Four and Paper Five that includes implementation of guideline recommendations for depression screening and referral in HNC patients.

INTRODUCTION TO PAPER TWO AND THREE: Screening and appropriate referral of patients with cancer for distress

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PAPER TWO: INTERVENTIONS TO IMPROVE SCREENING AND APPROPRIATE REFERRAL OF PATIENTS WITH CANCER FOR DISTRESS: SYSTEMATIC REVIEW PROTOCOL

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Associated Appendices:

Appendix   A4 PROSPERO registration for Paper Two and Paper Three
A5 PRISMA checklist for Paper Two
A6 Paper Two – Published manuscript
A7 Search strategy for Paper Two and Paper Three

PAPER TWO: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review protocol

ABSTRACT

Introduction: It is estimated that 35%–40% of cancer patients experience distress at some stage during their illness. Distress may affect cancer patients' functioning, capacity to cope, treatment compliance, QoL and survival. Best practice clinical guidelines recommend routine psychosocial distress screening and referral for further assessment and/or psychosocial supports for cancer patients. However, evidence suggests this care is not provided consistently.

Methods and analysis: We developed our methods following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Appendix A5). The review is registered with PROSPERO (Appendix A6) and any amendments to the protocol will be tracked. The primary aim of this systematic review is to examine the impact of interventions delivered in health care settings that are aimed at i) improving routine screening of patients for psychosocial distress and ii) referral of distressed cancer patients for further assessment and/or psychosocial support. The effectiveness of such interventions in reducing cancer patient psychosocial distress; and any unintended adverse effect of intervention will also be assessed. Data sources will include the bibliographic databases Cochrane Central Register of Controlled Trials; CENTRAL in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. Eligible studies must compare an intervention (or two or more interventions) in a health care setting to improve the rate of screening for psychosocial distress and/or referral for further assessment and/or psychosocial support for cancer patients with no intervention or 'usual' practice. Two investigators will independently review titles and abstracts, followed by full article review and data extraction. Disagreements will be resolved by consensus and if necessary, a third reviewer. Where studies are sufficiently homogenous, trial data will be pooled and meta-analyses performed.

PAPER TWO: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review protocol

INTRODUCTION

Rationale

Between 35%–40% of cancer patients experience distress at some stage during their illness (1). Despite this, distress is often unrecognised in cancer patients by clinicians (2). Psychological distress can arise in response to cancer related factors such as diagnosis and cancer progression (2). Distress may affect cancer patients' functioning, capacity to cope, treatment compliance, QoL and survival (3, 4) and increase the treatment burden to the medical team and health care system (5). Addressing distress in cancer populations is, therefore, an important health priority.

The importance of psychosocial care for cancer patients is recognised by professional associations and is included in clinical guidelines (5, 6). The NCCN *Clinical Practice Guidelines in Oncology: Distress Management* (3), and the National Institute for Clinical Excellence guidance manual, *Improving Supportive and Palliative Care for Adults with Cancer* (7) recommend routine screening for psychosocial distress and subsequent assessment or referral to appropriate services by those responsible for the care of patients with cancer. The Institute of Medicine report, *Care for the Whole Patient* recommends screening for distress and the development of a treatment plan with referrals as needed to psychosocial services (8). In 2015, the American College of Surgeons Commission on Cancer required cancer centres to implement screening programs for psychosocial distress as a new criterion for accreditation (9). Systematic reviews and meta-analyses on which these recommendations are based have demonstrated distress screening and referral improves the identification and management of psychosocial distress and reduces psychological morbidity in patients with cancer (4, 10).

PAPER TWO: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review protocol

Despite evidence based guideline recommendations, screening and referral of cancer patients for psychosocial distress is not routinely conducted by clinicians responsible for the clinical management of cancer patients (3, 11). While previous reviews have examined the Distress Thermometer (DT) (1) on cancer patients' outcomes such as QoL or depression (12-16) or the impact of patient reported outcome measures to improve identification of distressed patients and improve treatment decisions (17, 18) we are not aware of any previous systematic review of interventions to improve clinician provision of screening and appropriate referral of cancer patients per-se. Reviews of clinical practice change interventions more broadly suggests that a range of interventions may be effective in improving clinician provision of care consistent with guidelines recommendations such as educational strategies, audit and feedback, use of reminders and multiprofessional collaboration (19-21).

Objectives

In the absence of reviews particularly aimed at interventions to increase screening and referral for distress in cancer patients, the primary aims of the review are to determine the impact of interventions to improve clinician provision of screening and appropriate referral of cancer patients for distress. In particular, we will assess the impact of such interventions on:

i) improving screening of patients for psychosocial distress; and

ii) improving referral of cancer patients who screen positive on a measure of distress for further assessment and/or psychosocial support

The secondary aims of the review are to:

i) describe the effectiveness of such interventions on reducing cancer patient psychosocial distress; and

ii) describe any unintended adverse effects of such intervention.

METHODS AND ANALYSIS

The review methods are based on the PRISMA statement (22).

Eligibility criteria

Study characteristics

Types of studies

Inclusion criteria

Studies with the following study designs will be included:

- RCTs, including cluster RCTs;

- staggered enrolment trials or stepped-wedged trials;

- quasi-randomised trials

- quasi-experimental trials with comparison/control groups, including non-randomised pre-post (before-after) trials with one or more intervention and control groups, time-series/interrupted time-series trials (including multiple baseline trials) with independent control groups, preference trials and regression discontinuity trials;

- natural experiment studies that have a comparison group.

Any trials without parallel comparison or control groups will be excluded. There will be no restriction based on length of follow-up. There will be no restrictions based on year of study publication or language. Only studies published in peer reviewed scientific journals will be included.

Participants

Inclusion criteria

PAPER TWO: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review protocol

Participants could include:

i) Adult cancer patients who are about to undergo, are currently undergoing or have undergone medical treatment; including RT, chemotherapy, surgery or combined modality;

ii) Clinical staff members such as physicians, surgeons, and oncologists, nurses, and allied health professionals responsible for the care of cancer patients at any stage of treatment within primary and secondary health care settings such as hospitals, general practices or oncology clinics;

iii) Administrative staff of health services including hospital managers and quality assurance staff responsible for improving the delivery of health services to cancer patients; government or non-government cancer services or other organisations that may influence screening and referral of cancer patients.

Exclusion criteria

Studies which examine screening for psychosocial distress and/or referral for appropriate psychosocial support for carers of patients with cancer, or survivors of cancer, will be excluded. Studies reporting on cancer patients under the age of 18 will be excluded.

Types of Interventions

Inclusion criteria

Interventions will be included that are implemented in a health setting that aim to improve the rate of routine screening procedures for psychosocial distress and/or referral for appropriate psychosocial support in health care settings. Interventions could include quality improvement initiatives, education and training (23-25), performance feedback, prompts and reminders (19), implementation resources (26), financial

incentives (27) or the use of opinion leaders (23, 28). Interventions could be singular or multicomponent.

Consistent with the definition of distress provided by the NCCN (3) psychosocial distress will include any form of experienced distress, which may be due to emotional, psychological, social or spiritual factors. For the purposes of the review, distress screening is defined as the standardised brief assessment of patients to determine whether referral for more extensive assessment and/or psychosocial support services is warranted. Trials of interventions to improve the use of standardised screening tools or instruments with or without additional clinical judgement will be included. Studies using clinical judgement of psychosocial distress alone, without use of a formal screening tool will be excluded. Screening instruments could include traditional measures of psychosocial distress such as the DT (3), patient reported outcome measures of psychological distress including depression and anxiety, for example, the Hospital Anxiety and Depression Scale (HADS) (29) and measures of HRQoL that include a psychological distress component as a core component domain, for example, the MOS 36-Item Short-Form Health Survey (30). Administration of the screening instrument may be completed orally or via a paper-based questionnaire or computer/tablet questionnaire.

Referral for psychosocial support will include any written or verbal offer or direction of a patient for further review, consultation, assessment or treatment with any health professional including the primary oncology team or health service offering psychosocial support such as psycho-oncology services. Referral must be made as part

of the implemented intervention and based on the results of a distress screening instrument. The referral should not be based on clinical judgement alone.

Studies will be included if they implement either distress screening only or distress screening and appropriate referral. Interventions targeting a range of clinical practices such as treatment or management decisions, or medication prescription that also include screening for psychosocial distress and/or referral for appropriate psychosocial support will be included only when data for changes in screening and/or referral is reported separately from other outcomes. Studies where research staff conduct screening or referral will be excluded, as will trials of population-based community screening programmes.

Exclusion criteria

Studies using clinical judgement of psychosocial distress alone, without use of a formal screening tool will be excluded. Studies where research staff conduct screening or referral will be excluded, as will trial of population-based community screening programmes.

Comparisons

Comparisons will be included that are no intervention controls, 'usual' practice, or that are alternative interventions.

Outcomes

Primary outcomes:

i)   Any outcome measure reporting the provision of screening for psychosocial distress will be included (e.g. number or % of cancer patients screened). Such data may be obtained from medical record audits, client or clinician report, administrative data, audio recording or other sources.

ii)   and/or any outcome measure of the provision of referral for further assessment and/or psychosocial support (e.g. number or % of cancer patients referred). Such data may be obtained from medical record audits, client or clinician report, administrative data, audio recording or other sources such as records of referral service use by organisations providing psychosocial care for cancer patients.

Secondary outcomes:

i)   Any validated outcome measure psychosocial distress in the patients (e.g. distress outcome assessments (such as the Kessler Psychological Distress Scale) will be included (31).

ii)   Any outcome measure of unintended adverse effects or barriers of the intervention to patients, clinicians or health services such as stress in health professionals providing psychosocial screening and referral (32).

Information sources

Electronic databases

The following electronic databases will be searched for potentially eligible studies; the CENTRAL in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The Medline search strategy below will be adapted for other databases and will include filters used in other systematic reviews for population (cancer patients) (33), screening for distress (34) and referral (35) and psychosocial support (36).

Other sources

Studies will also be obtained from the following sources:

- Reference lists of included studies

PAPER TWO: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review protocol

- Hand searching of three relevant journals in the field (published in the last five years); Journal of the NCCN, Psychooncology and Supportive Care in Cancer

- Hand searching of conference abstracts published in the preceding two years from the International Psycho-Oncology Society and the Society of Behavioural Medicine

- A grey literature search using Google Scholar (published online in the last five years – the first 200 citations will be examined)

Search strategy

The search strategy for MEDLINE is in Appendix A7. This strategy will be adapted to the other electronic databases, with any modifications reported in the review manuscript.

Study selection

The titles and abstracts retrieved by electronic searches will be exported to a reference management database (Endnote version X6) to remove duplicates. Two reviewers will independently screen abstracts and titles. The reviewers will not be blind to the author or journal information. Screening of studies will be conducted using a standardised screening tool and will be pilot tested with a sample of articles before use. The abstracts of papers that are in a language other than English will be translated using Google Translate. If considered eligible or eligibility is unclear, professional translation of the full paper with be undertaken.

The full texts of manuscripts will be obtained for all potentially eligible trials for further examination. For all manuscripts, the primary reason for exclusion will be recorded and documented in the excluded studies table. Discrepancies between the two review

authors regarding study eligibility will be resolved by discussion and consensus and if necessary, a third reviewer.

Data extraction

The two review authors will independently extract data from the included trials using a pre-piloted data extraction form that will be developed based on recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (37). The data extraction form will be piloted before use. Discrepancies between reviewers regarding data extraction will be resolved by discussion and consensus and if necessary, include a third reviewer. Information will be transferred from data extraction forms into statistical software for meta-analyses.

Data items

The following information will be extracted:

- Authors, year and journal

- Study eligibility, study design, health care provider type (e.g. nurses), country, health care setting (e.g. oncology clinic)

- Patient characteristics and demographics including cancer site, cancer stage, age, sex, cancer treatment type, treatment status (pre/undergoing/post)

- Characteristics of the intervention, including the duration, intervention strategies, the theoretical underpinning of the study (if noted in the study), screening instrument

- Trial primary and secondary outcomes, including sample size, the data collection method, validity of measures used, any measures of client uptake or use of psychosocial support services following referral, effect size, measures of change in psychosocial distress

- Source(s) of research funding and potential conflicts of interest

- Number of participants per experimental condition as well as information to allow assessment of risk of study bias

Attempts will be made to contact the corresponding authors of included trials in instances where data is unavailable in the published manuscript.

Assessment of risk of bias

Two review authors will independently assess the risk of bias of all included trials in accordance with The Cochrane Collaboration's tool in the *Cochrane Handbook for Systematic Review of Interventions* (37). Disagreement between raters will be resolved by discussion and consensus with the involvement (if necessary) of a third review author. An additional criterion 'potential confounding' will be included for the assessment of the risk of bias in non-randomised trial designs (37).

Data analysis

Summary measures

There are a variety of commonly used screening instruments and scoring thresholds for psychosocial distress (34). As such, it is anticipated that there will be a range of different outcome measures reported across included studies, which may make meta-analysis of the data from these trials inappropriate, in which case, findings of included studies will be presented narratively. However, for the primary outcomes pertaining to provision of screening for distress and referral for further assessment and/or psychosocial care, and secondary outcomes, attempts will be made to conduct meta-analysis using data from included trials. For binary outcomes the standard estimation of the odds ratio and a 95% confidence interval will be calculated. For continuous data the

mean difference will be calculated where a consistent measure of outcome is used in included trials. Where different continuous measures are used to examine an outcome, the appropriateness of calculating a standardised mean difference will be considered. Authors of included trials will be contacted to provide additional information if any outcome data is unclear or missing.

Data synthesis and analysis

Meta-analysis will be performed using random effects models where suitable data and homogeneity exist (Isq <75%). Clustered trials will be examined for unit of analysis errors. An effective sample size will be calculated for use in meta-analysis for trials with unit of analysis errors without appropriate statistical adjustment. Data will not be pooled for trials of different study designs (e.g randomised and non-randomised designs). Sensitivity analysis will be performed by removing studies with a high risk of bias and by removing outliers contributing to statistical heterogeneity.

Assessment of study heterogeneity

Heterogeneity will be examined using visual inspection of box plots, forest plots and using the I^2 statistic. Where there is evidence of high heterogeneity (>Isq>75%), heterogeneity will be explored via subgroup analyses according to trial intervention and population characteristics. Funnel plots will be generated by statistical software to enable the assessment of publication bias.

Grading the strength of evidence

As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (37), the overall quality of evidence on outcomes will be presented using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach, which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication

bias. The overall quality of evidence will be rated at four levels: high, moderate, low and very low.

DISCUSSION

Despite guideline recommendations for psychosocial distress screening and referral in cancer, research suggests this care is not provided consistently (2, 38). Presently it remains unclear as to the effectiveness of interventions aimed at improving clinicians' provision of routine screening and referral for further assessment and/or treatment for psychosocial distress in cancer patients. The conclusions drawn from the present review, when disseminated to policy-makers, health care providers, and researchers will be helpful in identifying effective approaches for designing interventions aimed to improve the rate of routine provision of this care.

PAPER TWO: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review protocol

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PAPER THREE: INTERVENTIONS TO IMPROVE SCREENING AND APPROPRIATE REFERRAL OF PATIENTS WITH CANCER FOR DISTRESS: SYSTEMATIC REVIEW

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Associated Appendices:

Appendix   A4 PROSPERO registration for Paper Two and Paper Three

A7 Search strategy for Paper Two and Paper Three

A8 Quality assessment tool for quantitative studies

A9 Quality assessment tool for quantitative studies dictionary

PAPER THREE: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review

ABSTRACT

Objectives: The primary aim of the review was to determine the effectiveness of strategies to improve clinician provision of distress screening and referral of patients with cancer.

Design: Systematic review.

Data sources: Electronic databases (CENTRAL, MEDLINE, EMBASE, PsycINFO and CINAHL) were searched until July 2016.

Inclusion criteria: Population - Adult cancer patients and clinical staff members. Intervention - Any strategy that aimed to improve the rate of routine screening and referral for detected distress of cancer patients. Comparison - No intervention controls, 'usual' practice, or alternative interventions. Outcome – (Primary) any measure of provision of screening and/or referral for distress, (secondary) psychosocial distress, unintended adverse effects. Design - Trials with or without a temporal comparison group including randomised and non-randomised trials, and uncontrolled pre-post studies.

Data extraction and analysis: Two review authors independently extracted data. Heterogeneity across studies precluded quantitative assessment via meta-analysis and so a narrative synthesis of the results is presented.

Results: Five studies met the inclusion criteria. All studies were set in oncology clinics or departments and used multiple implementation strategies. Using GRADE, the overall rating of the certainty of the body of evidence reported in this review was assessed as very low. Three studies received a methodological quality rating of weak and two studies received a rating of moderate. Only one of the five studies reported a significant improvement in referrals.

PAPER THREE: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review

Conclusions: Current research provides inconsistent evidence from predominantly poor quality studies of the effectiveness of strategies to improve the routine implementation of distress screening and referral for cancer patients. The small number of trials to date combined with the low quality evidence highlights the need for well-designed studies to identify effective support strategies to maximise the potential for successful implementation.

PAPER THREE: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review

INTRODUCTION

Rationale

Distress interferes with the ability to cope with cancer treatment, and can include problems that are disabling such as depression, anxiety, panic and feeling isolated or in a spiritual crisis (1). Between 20% to 47% of cancer patients experience significant levels of distress (1). Distress can arise in response to cancer related factors such as diagnosis and cancer progression, pain and adverse effects of treatment (2). Distress in cancer patients may lead to non-adherence to treatment, poorer QoL and may negatively impact survival (1, 3) as well as increase treatment burden to the oncology team and health system (4). Therefore, recognising and treating distress in cancer populations is an important health priority.

Professional associations and clinical guidelines (5-9) including the NCCN *Clinical Practice Guidelines in Oncology: Distress Management* (1) recommend that those responsible for the care of cancer patients routinely screen for distress and, as appropriate, refer for further assessment and support. These recommendations are based on systematic reviews and meta-analyses that have demonstrated screening improves the timely management of distress (3, 10), improves adherence to treatment, reduces burden to the treatment team and can avoid progression to more severe anxiety or depression (1). Best practice guidelines recommend that distress be scored on a continuum from low to high using standardized tools in order to differentiate low to high levels of distress and inform treatment approach (1). For example, the NCCN Guidelines recommend use of the Distress Thermometer (DT), developed by the NCCN Distress Management Panel. The DT serves as an initial single-item question screen and scores of 4 or higher suggest a level of distress that has clinical significance. A member

of the key oncology team then identifies the key issues of concern and asks further questions to determine to which resources the patient should be referred (1). The Problem List, also developed by the NCCN Distress Management Panel, can accompany the DT and includes a 39-item Problem List and asks the patient to identify their problems in five different categories: practical, family, emotional, spiritual and physical.

Despite evidence based guideline recommendations, screening and referral of cancer patients for distress is not routinely conducted by clinicians responsible for the clinical management of cancer (1, 2, 11). Beginning in 2015, the American College of Surgeons Commission on Cancer has required cancer centres to implement programs for distress screening as a criterion for accreditation (42). A recent cross-sectional survey of 20 NCCN Institutions reported only 60% of services conducted outpatient distress screening, and even fewer services reported screening all patients (30%) as outlined in the NCCN standards (12). Systematic reviews of trials of strategies to improve depression or anxiety screening in primary care note that complex organisational interventions that incorporate multiple strategies are most effective in improving provision of care (13-15). Such strategies include clinician education, opinion leaders, patient specific reminders, enhanced role of nurses, academic detailing, integrating screening into routine clinical reviews and a greater degree of coordination between services (for example between primary and secondary care) (13-15). However, we are not aware of any previous systematic review of interventions to improve clinician routine provision of distress screening and appropriate referral of cancer patients per-se.

Objectives

PAPER THREE: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review

The primary aims of the review were to determine the impact of trials of strategies to improve clinician rate of screening and referral of patients with cancer for distress. In particular, we assessed the impact of such interventions on:

i) improving screening of patients for psychosocial distress; and

ii) improving referral of patients with cancer who screen positive on a measure of distress for further assessment and/or psychosocial support.

The secondary aims of the review were to:

i) describe the effectiveness of such interventions on reducing psychosocial distress of patients with cancer; and

ii) describe any unintended adverse effects of such an intervention.

METHODS AND ANALYSIS

The review methods were based on the PRISMA statement (16) (Appendix A7). The details of the methods have been reported elsewhere (17) and the protocol is registered with PROSPERO (registration number CRD42015017518) (Appendix A4).

Eligibility criteria

Study characteristics

Types of studies

Original studies including RCTs and non-randomised trials were included. Exclusion criteria were trials without parallel comparison or control groups. There were no restrictions based on length of follow-up, year of study publication or language. Studies could be published in peer review or grey literature.

Participants

Participants could include adult cancer patients and clinical staff members such as physicians and allied health professionals responsible for the care of cancer patients. Studies which examined screening for psychosocial distress and/or referral for carers of patients with cancer, or survivors of cancer, were excluded.

Types of Interventions

Interventions of strategies that aimed to improve the rate of screening procedures for distress and/or rate of referral for appropriate psychosocial support in health care settings were included. There are a range of potential strategies that could improve the likelihood of implementation of distress screening and referral in healthcare settings. For example, the Cochrane Effective Practice and Organisation of Care (EPOC) taxonomy is a framework for characterising educational, behavioural, financial, regulatory and organisational interventions within the topic of 'implementation strategies' (18) and includes 22 sub-categories. Examples of strategies within the taxonomy include educational materials, performance monitoring, local consensus processes and educational outreach visits. Included interventions could be singular or multicomponent. Studies using clinical judgement of psychosocial distress alone, without use of a formal screening tool were excluded. Referral for psychosocial support was defined as any written or verbal offer or direction of a patient for further review, consultation, assessment or treatment with any health professional, including the primary oncology team or health service, offering psychosocial support such as psycho-oncology services. Studies were included if they implemented either distress screening only or distress screening and appropriate referral. Studies where research staff conduct screening or referral were excluded.

Comparisons

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Studies with no intervention controls, 'usual' practice or alternative intervention comparison groups were included.

Outcomes

Primary outcomes:

    i)   Any measure of the provision of screening for distress (e.g. number or % of cancer patients screened); and/or

    ii)   Any measure of the provision of referral for further assessment and/or psychosocial support (e.g. number or % of cancer patients referred) by a clinician responsible for the management of a cancer patient.

Secondary outcomes:

    i)   Any validated outcome measure of change in distress levels in the patients (e.g. distress outcome assessments such as the Kessler Psychological Distress Scale) (19); and

    ii)   Any measure of adverse effects on patients, clinicians or health services; or barriers to performing screening such as clinician distress (20).

Information sources

Electronic databases

The following electronic databases were searched for potentially eligible studies published up until July 2016; CENTRAL in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The Medline search strategy (Appendix A7) was adapted for other databases and included filters used in other systematic reviews for population (cancer patients) (21), screening for distress (22) and referral (23) and psychosocial support (24).

Other sources

PAPER THREE: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review

Studies were also obtained from the following sources:

- Reference lists of included studies

- Hand searching of three relevant journals in the field (published in the last five years); Journal of the NCCN, Psychooncology and Supportive Care in Cancer

- Hand searching of conference abstracts published in the preceding two years from the International Psycho-Oncology Society and the Society of Behavioural Medicine

- A grey literature search using Google Scholar (published online in the last five years – the first 200 citations was examined)

Figure 1. PRISMA flow diagram

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Study selection
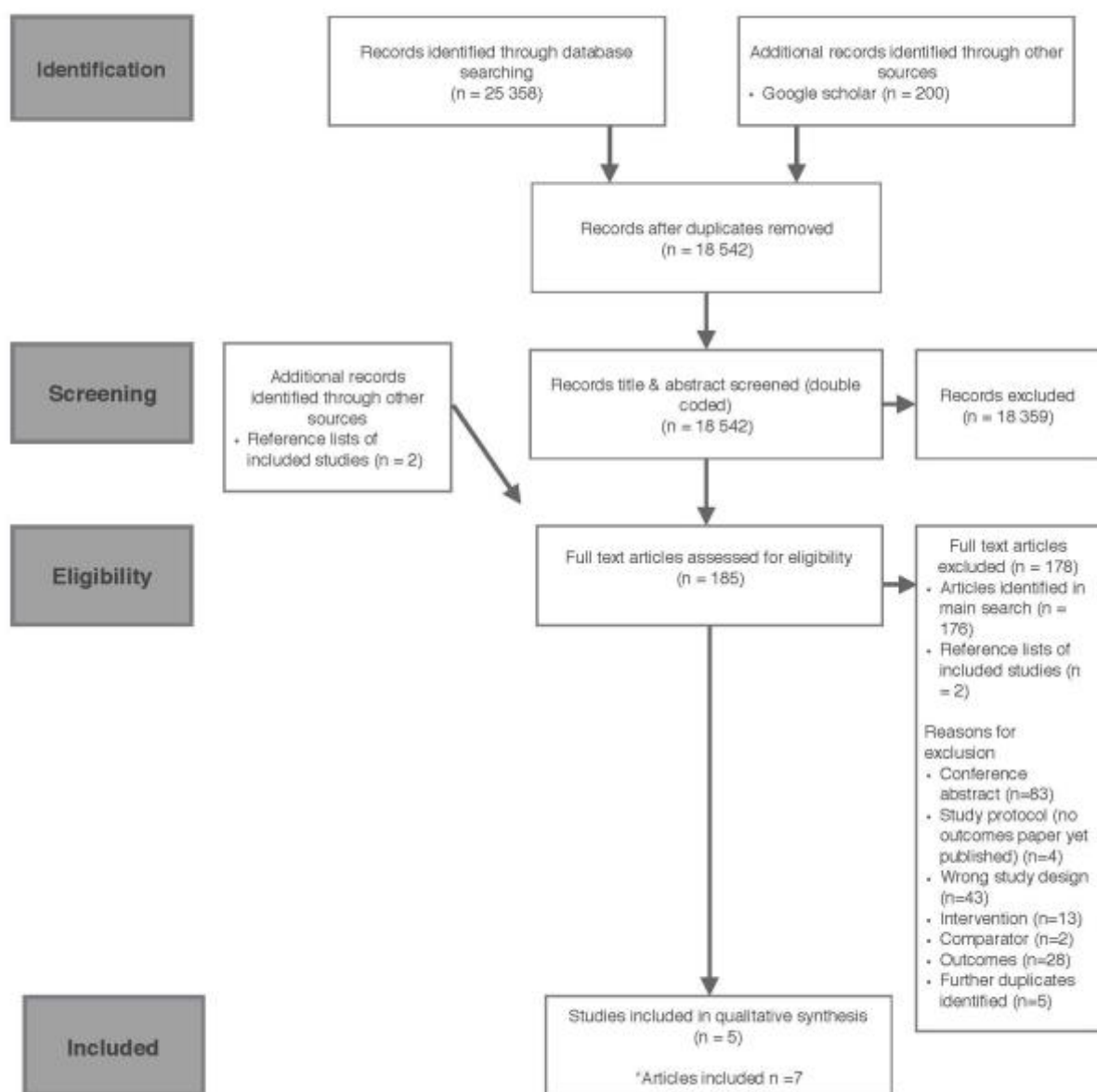
The titles and abstracts retrieved by electronic searches were exported to a reference management database (Endnote version X6) to remove duplicates. Two reviewers independently screened abstracts and titles using a standardised screening tool that was pilot tested with a sample of articles before use. The abstracts of papers that were in a language other than English were translated using Google Translate. If considered eligible or eligibility was unclear, professional translation of the full paper was undertaken. The full texts of manuscripts were obtained for all potentially eligible trials for further examination and independently screened by two reviewers. For all manuscripts, the primary reason for exclusion was recorded and is documented in Figure 1. Discrepancies regarding study eligibility were resolved by discussion and consensus.

Data extraction

Two review authors (KM and EF) independently extracted data from the included trials using a pre-piloted data extraction form that was developed based on recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (25). Discrepancies regarding data extraction were resolved by discussion and consensus.

Data items

Data was sought for the following variables:

- Authors, year and journal

- Study eligibility, study design, health care provider type (e.g. nurses), country, health care setting (e.g. oncology clinic)

- Patient characteristics and demographics including cancer site, cancer stage, age, sex, cancer treatment type, treatment status (pre/undergoing/post)

- Characteristics of the intervention, including the duration, intervention strategies, screening instrument

- Trial primary and secondary outcomes, including sample size, the data collection method, validity of measures used, any measures of client uptake or use of psychosocial support services following referral, effect size, measures of change in distress

- Number of participants per experimental condition

- Information to allow assessment of risk of study bias

Methodological quality assessment bias

Two review authors (KM and EF) independently assessed the risk of bias of all included trials using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP) for quantitative studies (26) (Appendix A8 and A9). The use of the EPHPP tool was a post hoc change from protocol due to the study designs included in the review. This tool covers any quantitative study design and includes components of intervention integrity (25, 27). Any discrepancies were resolved through discussion. The EPHPP assesses six methodological dimensions: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. These domains are rated on a three-point scale (strong, moderate, weak) according to pre-defined criteria and procedures recommended for tool use, and then given an overall global rating. Those with no weak ratings were given an overall rating of strong, those with one weak rating were given an overall rating of moderate and those with two or more weak ratings across the six domains were given an overall weak rating. Two additional methodological dimensions provided by the tool are intervention integrity and analyses and these were also completed by the reviewers.

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Data analysis

Summary measures

The small number of studies and differences in study design and primary and secondary outcomes reported in the included studies precluded the use of summary statistics to describe treatment effects. As such, the findings of included trials are described narratively.

Grading the strength of evidence

As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* (25), the overall quality of evidence on primary outcomes is presented using the GRADE approach, which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The overall quality of evidence was rated by two review authors (KM and EF) at four levels: high, moderate, low and very low.

RESULTS

A total of 18 542 citations were identified (after duplicates were removed) (Figure 1) for abstract and title screening. Just one study met the eligibility criteria (i.e. parallel control/comparison group). As such, and in an attempt to provide some evidence to guide researchers and practitioners regarding methods to improve patient distress screening and referral of cancer patients, we relaxed the design criteria and post-hoc rescreened all 18 542 citations and included studies with controlled trial designs without parallel control groups including uncontrolled pre post studies. The full text of 185 manuscripts were sought for further assessment against the review inclusion criteria (Figure 1). Of these,

Table 1. Trial characteristics

Study	Design	Study dates	Single-centre or multicentre	Setting	Country	Aim	Patient inclusion criteria	No. of patients	Mean age in years (SD)	Gender (male)	Tumour site/Tumour stage	Cancer treatment type/Stage of
Thewes et al. 2009 (34)	Pre post	NR.	Multicentre - 3 rural outpatient oncology clinics	Outpatient oncology clinics.	Australia	(i) Prospectively investigate the feasibility and acceptability of introducing a routine psychological screening program for rural oncology clinics; (ii) explore the impact of screening on rates and timeliness of referral to psychosocial services; and (iii) provide pilot data on the acceptability and utility of the DT as a screening tool within the rural Australian setting	(i) Newly diagnosed with malignant disease; (ii) 18 years of age or older; (iii) able to give informed consent; and (iv) able to read English proficiently.	Unscreened cohort – 40. Screened cohort – 43.	60.0 (10.5 SD).	54.0%	Colorectal 22.9%, Breast 30.1%, Lung 14.5%, Other 13.2%, Haematological 9.6%, Skin 6.0%, Unknown primary 3.6%, Localised/locally advanced 71.1%, Advanced or metastatic 28.9%.	Surgery 75.9%, chemotherapies 66.3%, RT 53%, endocrine therapies 32.5%. Newly diagnosed patients.
Braeken et al. 2009 (29), 2013 (30) & 2013 (31)	Cluster randomised controlled trial	April 2008 – October 2010.	Single	Institute Verbeeten (BVI) - a radiation oncology department (Tilberg).	The Netherlands	i) To study the effect of the SIPP on the number and types of referrals of cancer patients with psychosocial problems to psychosocial caregivers.	i) Receiving RT; ii) most common cancer types such as lung, prostate, bladder, rectum, breast, cervix, endometrial, skin and Non-Hodgkin; iii) 18 years of age or older; and iv) no metastases. Exclusion criteria: i) receiving palliative treatment, ≤ 10 fractions of RT; ii) unable to read and speak Dutch; and iii) unable to complete questionnaires.	Control group – 300. Intervention group – 268.	Control group 62.4 (10.7 SD), intervention group 62.4 (10.8 SD).	Control group 47.0%, intervention group 31.7%.	Prostate/Bladder 24.1%, Lung 11.3%, Breast 50.0%, Cervix/Endometrial 1.6%, Rectum 9.0%, Non-Hodgkin 9.0%, Lymphoma 1.7%, Skin 2.3%.	100% RT. SIPP1 before the first consultation prior to RT and SIPP2 before the consultation at the end of RT.
Ito et al. 2011 (28)	Pre post	UP: April 1 - September 30, 2006. PP: April 1 - September 30, 2007.	Single	Outpatient treatment center of the NCCH-E (Kashiwan oha, Kashiwa, Chiba).	Japan	To examine the usefulness (rate of referral) of a screening program modified for outpatients with cancer who are undergoing chemotherapy.	All consecutive cancer patients who began chemotherapy at the outpatient treatment center of NCCH-E in Japan.	UP – 478. PP – 520.	UP 61.4 (10.8 SD), PP 62.8 (10.9 SD).	UP 54.0%, PP 56.7%.	Lung 20.0%, Colon/rectum 18.2%, Breast 13.8%, Hematopoietic and lymphatic tissue 12.8%, Stomach 7.9%, Pancreas 10.2%, Esophagus 5.5%, Liver, bile duct, gall bladder 4.6%, Head and Neck 2.8%, Other 4.0% Reported for PP only: Stage I 2.5%, Stage II	Chemotherapy. Patients beginning chemotherapy at the outpatient treatment center of the NCCH-E.

Study	Design	Study period	Centre	Country	Setting	Objective	Population	Sample	Age	%	Tumour stage / Cancer type	Treatment / Additional notes
Zemlin et al. 2011(32)	Propsective consecutive study	NR.	Single	Germany	Clinic for Gynaecology of University of Marburg Hospital (Marburg).	To examine whether a screening and computer-based psycho-oncological clinical pathway can improve the diagnosis of breast cancer patients requiring psycho-oncological support according to current guidelines.	Breast cancer patients who were in stationary treatment.	Phase 1 - 236, Phase II – 384, Phase III - 247.	59.5 (12.2 SD).	0.6%	Breast carcinoma in situ 11.6%, Stage I 43.7%, Stage II 25.5%, Stage III 7.8%, Stage IV 11.2%; 9.6%, Stage III 20.8%, Stage IV or recurrent 67.1%	Screening occurred on day of admission. Stage of treatment NR.
Bauwens et al. 2014 (33)	Pre post	UP: May 2010. DB period June 2010.	Single	Belgium	Oncology Centre of the University Hospital (UZ Brussel).	To evaluate the impact of systematic screening with the DB on detection rates of patients with elevated distress and on rates of psychosocial referral compared to usual practice.	i) Ambulatory patients; ii) 18 years and older; iii) diagnosed with cancer; iv) sufficiently fluent in the languages of the study (Dutch or French); and iv) not affected by a cognitive disorder.	UP – 278, DB period – 304.	UP – 278, 58.92 (13.03 SD).	32.0%	Breast 43.9%, Lung 10%, Colon 8.6%, Prostate 3.4%, Gynaecological 3.4%, Brain 7.4%, Skin 9.5%, Other 9.5%; Local disease 33%, Locoregional disease 38.6%, Advanced disease 28.4%; Diagnosis 2.1%, active treatment curative intent 22.7%, active treatment palliative intent 53.0%, cured 9.8%, remission (partial/complete) 3.3%, palliative care 0.3%, wait and see 5.0%, recent recurrence 3.8%	No treatment 24.3%, surgery 3.1%, RT 1.7%, chemotherapy 43.3%, medication 18.9%, RT + chemotherapy 2.1%, chemotherapy + medication 5.8%, RT + medication 0.7%

NR, not reported; DT, Distress Thermometer; UP, usual care period; PP, program period; DB, Distress Barometer; NCCH-E, National Cancer Center Hospital East; DT, Distress Thermometer; SIPP; Screening Inventory Psychosocial Problems; RT, RT.

178 were considered ineligible following the trial screening process. Seven publications describing five trials were included in the review.

Included studies

Types of studies

A description of the trial characteristics of included studies is provided in Table 1. One study was conducted in Japan (28), one in the Netherlands (29-31), one in Germany (32), one in Belgium (33) and one in Australia (34). Studies were published between 2009 and 2014. There was considerable heterogeneity in the participants, interventions and outcomes (clinical heterogeneity) of included studies.

Health providers

All studies were set in oncology clinics or departments. In regards to the healthcare providers responsible for conducting the distress screening and/or referral, one study targeted nurses (34), one targeted radiation oncologists (29-31), one required pharmacists to perform the screening (28), one study involved both specialised breast care nurses and doctors (32) and one study utilised oncologists (33).

Interventions

All trials used multiple implementation strategies. The EPOC subcategories used to classify the implementation strategies employed by included studies in the review are provided in Table 2. Using EPOC taxonomy descriptors, all trials included educational materials and educational meetings, with two trials using only these strategies (33, 34) (Table 3). One trial utilised these strategies with the addition of educational outreach visits (29-31). One study used a combination of educational materials, educational meetings, educational outreach visits and reminders (28). One study tested an intervention

consisting of organisational culture, continuous quality improvement, educational materials, educational meetings and reminders (32).

Outcomes

Implementation of distress screening and/or referral was primarily assessed using reviews of patient medical records (28-32, 34), however one study did not report the data collection method (33). None of the studies reported which staff completed the medical record reviews. All trials reported the rates of referral for supports for those patients identified as distressed, however none of the studies examined the improvement in rates of distress screening. Change in distress levels were reported in one study (29-31). No studies included a measure of potential adverse effects.

Study design characteristics

One of the included studies was a cluster RCT (29-31), four were pre post studies (28, 33, 34) and one was a prospective consecutive study (32). The cluster RCT compared an intervention to a usual care control (29-31), three studies compared a screening program period to a usual care period (28, 33, 34) and one trial compared a screening program phase to a two-phase non-screening period (32).

Methodological quality assessment

Individual ratings for each study against the six methodological criteria from the EPHPP tool and the assigned global rating are reported in Table 6. Overall, three studies received a methodological quality rating of weak (32-34) and two studies received a rating of moderate (28-31). For three of the four non-randomised studies (32, 34, 35), it was unclear whether confounders were adequately adjusted for and for the majority of studies, blinding of outcome assessors or study participants was not described. While most studies reported medical record reviews for the data collection method, no reference was made

to their validity or reliability as an outcome measure, nor was a description of who conducted the audits provided, resulting in weak ratings for all studies. All studies were judged as using analyses as appropriate to study design.

Effects of intervention on distress screening and/or referral

None of the included trials reported on the effects of strategies to improve rates of distress screening provision (Table 4). Only one of the five studies reported a significant improvement in rate of referrals (32). Zemlin et al. (32) reported a significant positive trend for the number of patients that were informed/offered psycho-oncological interview (t = 22.40, df = 2, p <0.001). The effects of interventions are presented according to the

Table 2. Definition of EPOC subcategories

EPOC subcategory	Definition
Educational materials	Distribution to individuals, or groups, of educational materials to support clinical care, i.e. any intervention in which knowledge is distributed. For example, this may be facilitated by the internet, learning critical appraisal skills; skills for electronic retrieval of information, diagnostic formulation; question formulation.
Educational meetings	Courses, workshops, conferences or other educational meetings.
Educational outreach visits or academic detailing	Personal visits by a trained person to health workers in their own settings, to provide information with the aim of changing practice.
Reminders	Manual or computerised interventions that prompt health workers to perform an action during a consultation with a patient, for example computer decision support systems.
Organisational culture	Strategies to change organisational culture.
Continuous quality improvement	An iterative process to review and improve care that includes involvement of healthcare teams, analysis of a process or system, a structured process improvement method or problem solving approach, and use of data analysis to assess changes.

Table 3. Intervention description

Study	Healthcare providers	Distress screening tool	Referral criteria	Training	Intervention	Control/Comparison	Implementation Strategies
Thewes et al. 2009 (34)	Nurses	The DT - a single item screening measure that identifies level and causes of distress. Respondents are asked to indicate their level of distress in the past week on an 11-point scale ranging from 0 ('None') to 10 ('Extreme').	Screening cohort - for psychosocial staff participated in a 2 hour training session covering the screening procedure and suggestions for how to discuss the results of screening with patients who scored above cut-off.	Nursing and psychosocial staff completed immediately before an initial oncologist rural clinic appointment or chemotherapy education session.	Distress screening was completed immediately before the SPHERE-Short at baseline; a 12-item questionnaire measuring common psychological and somatic distress developed and validated in Australia. The SPHERE- Short has 2 subscales: PSYCH-6 and somatic symptoms. A score of ≥2 on the PSYCH-6 subscale indicates a likely case of psychological disorder.	All participants completed the SPHERE-Short at baseline; a 12-item questionnaire measuring common psychological and somatic distress developed and validated in Australia.	Educational materials, educational meetings.
Braeken et al. 2009 (29), 2013 (30) & 2013 (31)	Radiation oncologists	The SIPP - a short, valid and reliable 24-item self-reported questionnaire that systematically identifies psychosocial problems in Dutch cancer patients. Items are rated on a 3-point scale of 0 (no) to 2 (yes). Higher scores indicate poorer functioning.	Intervention: Potential referral to a psychosocial caregiver was based on the scores of the SIPP in combination with the radiation oncologist's judgement. Control: According to the radiation oncologist's judgement about the presence or absence of psychosocial problems in patients.	Before the start of the study, the radiation oncologists in the experimental condition were trained in using and interpreting the SIPP during a 1 hour training session. Training was given by the researcher and two social workers with experience in using and discussing the SIPP.	Patients received the SIPP just before the first and last consultation with the radiation oncologist. Psychosocial problems were discussed with the patient during the consultation and referral to a psychosocial caregiver occurred only with the permission of the patient. The radiation oncologists were stratified according to general percentages of incoming patients they referred in 2006–2007 and then randomised to experimental or control condition.	Care as usual - no recent guidelines for the systematic assessment of psychosocial problems in cancer patients existed at the Institute Verbeeten. The radiation oncologist was able to refer patients to psychosocial caregivers (social workers) at the Institute Verbeeten based on their clinical judgement.	Educational materials, educational meetings, educational outreach visits.
Ito et al. 2011 (28)	Pharmacists	The DIT - a 2 item, self-administered rating scale. Each 'distress' and 'impact' question is scored using an 11-point Likert scale, with scores ranging from 0 to 10 and a high score indicating an unfavourable status.	PP - if a patient scored equal to or more than each cut-off point (≥ 4 for distress and ≥ 3 for impact) the screening result was regarded as positive.	Before implementing the screening program, all the pharmacists attended a 2 hour lecture given by a trained psychiatrist regarding the epidemiology,	Pharmacists providing instructions to patients beginning chemotherapy at their first and second visit also provided information regarding the Psychiatric Service using a brief pamphlet and invited the patients to complete the DIT.	UP was not described in detail.	Educational materials, educational meetings, educational outreach visits, reminders.

Study	Participants	Screening measure	Description of intervention	EPOC category
			impact, risk factors, under-recognition, and appropriate management of psychiatric disorders in cancer patients. Additionally, the pharmacists underwent role-play training to learn how to implement the DIT and to give recommendations for psychiatric referral. / The pharmacist then completed the screening program sheet, which is a record of the patient's DIT scores. The pharmacist recommended a consultation with the Psychiatric Service to all the patients with a positive screening result and recorded the screening results on the medical chart.	
Zemlin et al. 2011 (32)	BCN's and doctors	The HADS - scores of more than 13 indicate clinically suspected psychological distress.	Phase I – BCN's and doctors asked the patient about their interest in a psycho-oncological consultation where they felt necessary. Phase II – BCN's asked all patients about their interest in a psycho-oncological consultation on day of admission. Phase III – patients were referred to a psycho-oncological interview if i) they scored > 13 on the HADS; ii) the doctor had a clinical impression that the patient required referral; or iii) the patient desired referral. / Certified training courses for clinicians, gynaecologists and psychotherapists as well as other professional groups of the inpatient and outpatient network were carried out. / In Phase III, all patients completed the HADS questionnaire. The BCN evaluated the HADS and informed the patients about the possibility of a psycho-oncologic initial interview. The BCN passed the evaluated HADS sheet to the physician. For those patients with psycho-oncological need (threshold HADS score and/or clinically suspected treatment oriented psychological distress) the doctors recommended a psycho-oncological interview. Each patient with a desire for psycho-oncological care was logged and offered initial interview (regardless of HADS score). / In Phase I, BCN's and doctors asked the patient about their interest in a psycho-oncological consultation where they felt necessary. In addition, all patients received information on psychosocial support options.	Organisational culture, continuous quality improvement, educational materials, educational meetings, reminders.
Bauwens et al. 2014 (33)	Seven oncologists	The DB - comprises three parts: 1. The DT (described above). The VAS was slightly adapted by using a background colour effect with anchors labelled 'no distress' through 'moderate distress' and 'extreme distress'. 2. The CCS, which consists of 10 items that are rated on a coloured 5-point scale. Patients are required to rate the	UP condition - oncologists used their own VAS assessment of distress to decide on an eventual referral. Whereas in the DB condition, they were given a written explanation on how to interpret DB results. Also in the DB condition, the cut-off point for the DB (Distress Thermometer ≥4 and elevated CCS was used by the / In a collective 1 hour session held shortly before the DB condition, oncologists were instructed in using the DB and were given a written explanation on how to interpret DB results. Also in the DB condition, oncologists had a form with three other yes/no questions: (2) if they considered referral necessary, (3) if they actually gave an advice for referral and / Two week period DB condition - The DB was administered before the consultation with the oncologist. Also in the DB condition, oncologists had a form with four other questions: (1) their rating of patients' distress on a VAS (0-10), (2) if they considered referral necessary, / 2 week period UP condition - The DB was administered after the consultation with the oncologist. Also in the UP condition, oncologists had a form with four other questions: (1) their rating of patients' distress on a VAS (0-10), (2) if they considered referral necessary,	Educational materials, educational meetings.

how much each of a list of sources of distress has been troubling them lately. 3. Additional Wish-Needs Questions: 4 additional questions regarding complaints and needs for further medical information and/or support.	oncologists for this purpose.	(4) if referral was accepted by patients.	(3) if they actually gave advice for referral and (4) if referral was accepted by patients.

BCN, breast care nurse; DT, Distress Thermometer; DIT, Distress and Impact Thermometer; HADS, Hospital Anxiety and Depression Scale; DB, Distress Barometer; VAS, Visual Analogue Scale; CCS, Coloured Complaint Scale; PP, program period; UP, usual care period; SIPP, Screening Inventory Psychosocial Problems; SHPERE-Short, Somatic and Psychological Health Report Short form; PSYCH-6, psychological symptoms.

Table 4. Primary outcomes

Study	Distress screening Measure; Results		Referral Measure; data collection method	Results
	Measure; data collection method	Results		
Thewes et al. 2009 (34)	Proportion of patients screened. NR.	Pre-screening phase – proportion of patients screened (using any distress screening tool) was not reported. Screening phase – all patients were screened using the DT.	Proportion of patients referred in the pre-screening phase compared to the screening phase. Review of referral records and databases.	Pre-screening phase - Of the 8 PSYCH-6 cases in the pre-screening phase, 6 were referred to a CCC and 5 to a social worker/psychologist. Screening phase – 10/19 (53%) patients that met the DT cutoff were referred to a social worker or psychologist (11 of 14 PSYCH-6 cases were referred to the CCC and 8 to a social worker/psychologist).
Bracken et al. 2009 (29), 2013 (30) & 2013 (31)	Proportion of patients screened. NR.	Control group – proportion of patients screened (using any distress screening tool) was not reported. Intervention group – 263/268 (98%) were screened using the SIPP before the first consultation. 250/268 (96%) were screened using the SIPP before end of RT consultation.	The number of referrals of patients with psychosocial problems to psychosocial workers at the Institute Verbeeten and/or to external health care providers (e.g. psychologists, psychiatrists). Three dichotomous outcome variables (yes/no) during the first 3 months, the last 9 months, and the total study period. Measured at 3 and 12 months after baseline assessment with a self-developed questionnaire by the patient and from registration records of the psychosocial caregivers at the Institute Verbeeten.	First 3 months - Control group 29/300 (9.7%) vs intervention group 34/268 (12.7%) patients referred (NS). Last 9 months – Control group 24/300 (8%) vs intervention group 19/268 (7.1%) patients referred (NS). Group differences in these outcomes were analysed using Generalized Estimating Equations with patients at level 1 and radiation oncologists at level 2. All models were adjusted for baseline differences with respect to gender and cancer diagnosis. Analyses were taken on an intention-to-treat principle. Numbers of referrals did not differ significantly between the intervention and control group at 3 months (β =1.41(SE±.81),

Study	Outcome – screening	Outcome – referral	Results	Analysis
Ito et al. 2011 (28)	Proportion of patients screened. NR. PP – 441/520 (84.8%). UP – proportion of patients screened (using any distress screening tool) was not reported.	Proportion of patients referred to the Psychiatric Service and treated for MDD or AD among all the outpatients who had begun a new chemotherapy regimen within 3 months of their visit to the outpatient clinic. Data extracted from patients' medical charts and the computerised database of the electronic medical record at NCCH-E.	UP – 5/478 (1.0%) vs PP – 15/520 (2.7%) patients referred to the Psychiatric Service with subsequent confirmed and treated for MDD or ADs ($p = .46$).	Retrospective cohort analysis (Chi-squared test comparing patients treated during the pp with historical control data gathered during the UP). 9 months (β =-1.41(SE±1.21) or overall months (β =-.67(SE±.78).
Zemlin et al. 2011 (32)	Proportion of patients screened. NR. Proportion of patients screened in Phase I or II screened (using any distress screening tool) was not reported. All patients in Phase III were screened using the HADS.	Proportion of patients offered referral for psycho-oncological interview. Medical records.	Phase I – 194/236 (82.2%) vs Phase II 344/384 (89.6%) vs Phase III 236/247 (95.5%) were informed/offered the psycho-oncological interview. There was a significant positive trend for the number of patients informed about the psycho-oncological care available ($t = 22.40$, $df = 2$, $p <0.001$).	Univariate data analysis. Cochran-Armitage test.
Bauwens et al. 2014 (33)	Proportion of patients screened. NR. UP condition – all patients were screened with the DB after consult with oncologist (therefore not used as part of the referral decision). DB condition – all patients were screened with the DB prior to consult with the oncologist.	Necessary referrals (UP condition: referrals necessary as per oncologists' VAS ratings, DB condition: referrals necessary for all patients with distress according to the DB). Self-assessment. Referrals made (UP condition: proportion of patients for whom referral was considered necessary by the oncologists and were actually referred to psychosocial care, DB condition: proportion of patients with elevated distress that were referred). Self-assessment.	UP condition – 13.8% of patients with elevated distress (or 5.4% of all patients), DB condition - 100% of patients with distress (or 41.6% of all patients). UP condition – 6/15 patients, DB condition - 85/123 patients.	

NR, not reported; DT, Distress Thermometer; UP, usual care period; SIPP, Screening Inventory Psychosocial Problems; DB, Distress Barometer; MDD, Major Depressive Disorder; AD, Adjustment Disorder; NCCH-E, National Cancer Center Hospital East; VAS, visual analogue scale; CCC, cancer care coordinator; NS, not significant.

implementation strategies (classified using the EPOC taxonomy) employed by included studies.

Educational materials and educational meetings

Two studies examined the impact of educational materials and educational meetings on distress screening or referral (34, 35). Thewes et al. (34) conducted a pre post trial testing the feasibility and acceptability of introducing a routine psychological screening program using the DT to improve screening rates and timeliness of referral to psychosocial services in three rural outpatient oncology clinics in Australia. Nursing and psychosocial staff participated in a two-hour training session (educational meetings and educational materials) covering the rationale for screening, the screening instrument and the study procedure. The impact of the intervention on distress screening was not explicitly reported (i.e. the control period rates of screening). Five of eight cases (according to predefined PSYCH-6 cutoff criteria) and ten of 19 cases (according to DT cutoff) were referred to a social worker or psychologist in the control and intervention periods respectively. Due to the small number of cases, significance testing of differences between the pre-screening and screening phases was not conducted.

Bauwens et al. (33) conducted a pre post study to evaluate the impact of systematic screening with the Distress Barometer (DB) on detection rates of elevated distress and on rates of psychosocial referral at an oncology centre in Belgium. Oncologists were instructed in using the DB and given a written explanation (educational materials) on how to interpret the DB results in a collective one hour session (educational meetings). As this study did not aim to improve rates of distress screening, but focused on oncologist detection of distress and subsequent referral, all patients were screened using the DB in both conditions. Consequently, the rates of distress screening prior to the study,

conducted by oncologists or other professional staff, compared to the study period are unknown. Of those patients for whom referral was considered necessary, 40% in the usual care condition and 69% in the DB condition were actually referred to psychosocial care. The authors did not conduct an analysis to determine if there was a significant difference in these rates, however concluded that the implementation of screening using the DB led to increased numbers of referrals to psychosocial professionals.

Educational materials, educational meetings and outreach visits

Braeken et al. (29-31) conducted a cluster RCT to study the effect of the implementation of the Screening Inventory Psychosocial Problems (SIPP) on the number and types of referrals of cancer patients to psychosocial caregivers in a radiation oncology department in the Netherlands. Radiation oncologists were randomised to a control or intervention group. Those in the intervention group were trained by a researcher and two social workers with experience in using and interpreting the SIPP during a one hour training session (educational meetings, educational materials and educational outreach visits). The study found no significant intervention effects were observed for the total number of patients referred to psychosocial care providers at any of the assessment time points (first three months, the last nine months and the total study period).

Educational materials, educational meetings, educational outreach visits and reminders

Ito and colleagues (28) conducted a pre post trial to examine the usefulness of a screening program (using the distress and impact thermometer; DIT) modified for cancer patients undergoing RT at an outpatient cancer treatment center in Japan. Prior to the screening phase, all pharmacists attended a two hour lecture and (educational meetings) given by a trained psychiatrist (who also met with the pharmacists monthly; educational outreach

visits) and underwent role play training to learn how to implement the DIT and referral for those patients scoring above the predetermined cutoff, (educational materials). When providing instructions to patients beginning chemotherapy and at the second visit, pharmacists invited patients to complete the DIT and a screening program sheet was completed by the pharmacists (reminders). The number of patients screened prior to the implementation of the screening program using the DIT or other measure was not assessed and 84.8% of patients were screened using the DIT in the intervention phase. The proportion of patients referred to the Psychiatric Service (and were subsequently confirmed to have major depression or adjustment disorder) during the screening program period compared to the usual care period was not significantly different between the two periods (2.7% during the program-period vs 1.0% during the usual care-period, $p = 0.46$).

Educational materials, educational meetings, reminders, organisational culture, continuous quality improvement

One study examined the effect of educational materials, educational meetings, reminders, organisational culture and continuous quality improvement on improvement in distress screening or referral. The trial by Zemlin et al. (32) was a prospective consecutive study that examined whether a screening and computer based psycho-oncological clinical pathway could improve the identification of breast cancer patients requiring psycho-oncological support at a gynaecology clinic in Germany. Prior to the introduction of the program, certified training courses were held for clinicians, gynaecologists and psychotherapists as well as other professional groups (educational meetings, educational materials, organisational culture) and every three to four months, cross-departmental meetings between psychology and gynaecology departments were held (continuous quality improvement). The authors described the trial in three phases; in phase one, breast care nurses and doctors asked the patient about their interest in a psycho-oncological

consultation where they felt necessary, and in phase two the nurses asked this of patients on the day of their admission. In phase three, the nurses conducted screening using the HADS with all patients and passed the HADS sheet to the physician (reminders). A predetermined cutoff indicated if referral was required. The proportion of patients screened with the HADS during phase three was 100%. The number of patients screened in phase one or two using the HADS or other measure was not assessed. The authors reported a significant positive trend for the number of patients offered referral for psycho-oncological care between phase one and three (t = 22.40, df = 2, p <0.001).

Secondary outcomes

Psychosocial distress

Only one study compared patients' levels of distress at follow-up using the distress screening measure implemented (Table 5). Braeken et al. (29-31) found no significant intervention effects as measured by the HADS for patients' psychological distress at three months or 12 months after baseline, nor dichotomous distress outcomes (no distress or at least moderate distress) at three months, or 12 months after baseline.

Reported adverse consequences

No study explicitly assessed whether the intervention had adverse effects.

Quality of the evidence

Using GRADE, the overall rating of the certainty of the body of evidence reported in this review was assessed as very low. The primary outcomes examined were downgraded one level to reflect high risk of bias and further downgraded two levels due to clinical heterogeneity and inconsistency in reporting either rates of distress screening or referral

Table 5. Secondary outcomes

Study	Measure; data collection method	Results
Braeken et al. 2009 (29), 2013 (30) & 2013 (31)	Extent of psychological symptoms at 3 months and 12 months after baseline. Measured with the HADS and the GHQ-12 (assesses with 12 items whether the patient considers him- or herself better, the same, worse or much worse over the previous four weeks than he/she "usually" is. Total scores range from 0 to 12). Patients complete these self- reported questionnaires at baseline and at 3 and 12 months after the baseline period.	Mixed effects' modelling. No significant intervention effects were observed for patients' extent of psychological distress. (3 months after baseline mean psychological distress score control group 2.85 vs intervention group 2.74, $p = 0.19$; 12 months after baseline mean psychological distress score control group 2.14 vs intervention group 1.96, $p = 0.12$).
	Group differences in the proportion of dichotomous distress outcome (no or at least moderate distress) at 3 months and 12 months after baseline. Measured with HADS and GHQ-12.	Generalised estimating equations. No significant intervention effects were observed for proportion of patients with distress (3 months after baseline control group 39% vs experimental group 38.4%, $p = .036$; 12 months after baseline control group 24.7% vs intervention group 24.3%, $p = 0.39$).

HADS, Hospital Anxiety and Depression Scale; GHQ-12, Goldberg's General Health Questionnaire-12 item version.

Table 6. Ratings of methodological quality: strong (S), moderate (M) and weak (W)

Study	Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals	Global rating
Thewes et al. 2009 (34)	Moderate	Moderate	Weak	Moderate	Weak	Moderate	Weak
Braeken et al. 2009 (29), 2013 (30) & 2013 (31).	Moderate	Strong	Strong	Moderate	Weak	Strong	Moderate
Ito et al. 2011 (28)	Moderate	Moderate	Strong	Moderate	Weak	Moderate	Moderate
Zemlin et al. 2011 (32)	Moderate	Moderate	Weak	Moderate	Weak	Moderate	Weak
Bauwens et al. 2014 (33)	Moderate	Moderate	Weak	Weak	Weak	Weak	Weak

across both control and intervention periods. Since indirectness and imprecision also lowers the quality of the evidence, we downgraded two further levels on that basis. We found the quality of evidence to be of weak to moderate quality due to risk of bias using the EPHPP (Table 6), which identified a number of limitations, particularly among the pre post studies in regards to controlling for potential confounders.

DISCUSSION

This review sought to assess the impact of trials of strategies to improve clinician provision of screening of patients for distress; and referral for further assessment and/or psychosocial support where necessary. The review identified just one trial that met the prospectively registered inclusion criteria of having a parallel control trial design. When these criteria were relaxed to include those with a non-parallel control group a further four trials were included. None of the included trials reported on the effects of strategies to improve distress screening, and the intervention in just one trial was effective in improving the rates of referral for psycho-oncological support for distressed patients. Such findings highlight the sparse evidence base for this important element of cancer patient care, and leave health services and cancer professionals with little clear guidance of strategies to improve provision of these elements of care to their patients.

Our findings are consistent with previous systematic reviews of trials aiming to improve depression or anxiety screening in primary care that have found that improvement in care provision is more likely when complex organisational change strategies are used, such as coordination between departments, enhanced role of nurses and performance feedback, in addition to clinician education (13-15). The trial by Zemlin et al. (32) was the only study included in the review to adopt a comprehensive implementation approach, and the

only to report significant improvement in referral of cancer patients for distress. Implementation strategies employed by other trials were primarily based on one off training and resource provision, suggesting that such support is insufficient. Comprehensive implementation strategies may be more likely to improve care given their greater capacity to address various barriers to screening and referral. Further research identifying they key barriers to such care, and the best strategies to address them in cancer services is therefore warranted.

Surprisingly, none of the included studies examined the impact of strategies to improve the rate of clinician provision of distress screening. Such a finding is of concern. Screening is a necessary pre-requisite to appropriate referral of cancer patients to psychological support. As screening for distress in cancer populations is low across jurisdictions (12), improving this form of care should represent a priority. Previous studies have used novel technologies to prompt screening by clinicians (36-38). Such approaches should be examined in robust trial designs in cancer settings that allow for their impact on improving the rate of routine clinician provision of distress screening to be determined.

A number of methodological aspects of the study warrant highlighting and should be considered when interpreting the study findings. As far as the authors are aware, this is the first systematic review to examine the impact of interventions of strategies to improve the rate of clinician provision of distress screening and appropriate referral in cancer patients. The review was prospectively registered, followed a peer reviewed protocol and included a comprehensive search strategy examining over 18000 citations. There was substantial clinical and methodological heterogeneity in the included studies.

Classification of EPOC taxonomy implementation strategies was also difficult due to the lack of detail reported on intervention components in the studies. Furthermore, all but one of the included studies were pre post trials. Such characteristics of the included studies precluded quantitative synthesis of the effects of these strategies.

Conclusions

The findings of this review suggest that there is considerable scope to improve implementation of distress screening and referral in cancer settings in order to establish a strong evidence base for future successful interventions. Implementation of distress screening and appropriate referral needs to be employed using a systematic method and assessed with appropriately controlled studies in order to determine the most effective approaches. Better reporting of outcomes and more detailed description of intervention components need to be prepared.

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PAPER THREE: Interventions to improve screening and appropriate referral of patients with cancer for distress: Systematic review

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IMPROVING CARE
FOR PATIENTS
WITH
HEAD AND NECK
CANCER

PAPERS FOUR & FIVE

INTRODUCTION TO PAPER FOUR AND PAPER FIVE

Paper One presented rates of health behaviour and affect risk factors (tobacco smoking, alcohol use and depression) in a sample of HNC patients, the population targeted in this body of work. Given the international recognition of the importance of recognising and treating distress in cancer patients (1) and the over representation of mental illness in the HNC population (2, 3), Paper Two and Paper Three assessed the impact of interventions to improve clinician provision of screening of patients for psychosocial distress and referral for further assessment and/or psychosocial support where necessary. The findings made apparent the need for robust studies to identify effective support strategies to maximise the potential for successful implementation. The one included study (4) in the review findings presented in Paper Three that reported a significant improvement in referral for distress employed the most comprehensive practice change strategy according to the EPOC taxonomy (5): educational materials, educational meetings, reminders, strategies to change organizational culture and continuous quality improvement. This finding aligned with the growing body of evidence for implementation science that indicates multi-component practice change strategies are effective in overcoming system barriers and translating best practice guideline knowledge into clinical practice (6, 7).

Within HNC care, guidelines recommend that a dietitian should be part of the multidisciplinary team for treating patients (8, 9). Recently developed Australian dietetic guidelines specific to HNC patients make a number of recommendations, including screening for distress and referral for further support (8). Paper Four presents the protocol for the major study of this body of work; clinical practice change strategies embedded within a RCT that aimed to test the effectiveness of the Eating As Treatment

(EAT) intervention. EAT is a dietitian-delivered intervention to prevent malnutrition in patients with HNC undergoing RT at five Australian hospital sites. The clinical practice change strategies were employed to improve the implementation of best practice guideline recommendations for the nutritional management of HNC patients and subsequently improve HNC patient care. The inclusion of multiple evidence based practice change strategies and theoretical framework was informed by the findings of Paper Three and the body of evidence supporting the use of comprehensive strategies to address barriers to guideline implementation.

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PAPER FOUR: EATING AS TREATMENT (EAT) STUDY PROTOCOL: A STEPPED-WEDGE, RANDOMISED CONTROLLED TRIAL OF A HEALTH BEHAVIOUR CHANGE INTERVENTION PROVIDED BY DIETITIANS TO IMPROVE NUTRITION IN PATIENTS WITH HEAD AND NECK CANCER UNDERGOING RADIOTHERAPY

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Associated Appendices:

Appendix   A10 Paper Four - Published manuscript

A11 Study principle prompts

ABSTRACT

Introduction: Maintaining adequate nutrition for HNC patients is challenging due to both the malignancy and the rigours of radiation treatment. As yet, health behaviour interventions designed to maintain or improve nutrition in patients with HNC have not been evaluated. The proposed trial builds on promising pilot data, and evaluates the effectiveness of a dietitian-delivered health behaviour intervention to reduce malnutrition in patients with HNC undergoing RT: EAT.

Methods and analysis: A stepped-wedge cluster randomised design will be used. All recruitment hospitals begin in the control condition providing treatment as usual. In a randomly generated order, oncology staff at each hospital will receive two days of training in EAT before switching to the intervention condition. Training will be supplemented by ongoing supervision, coaching and a two-month booster training provided by the research team. EAT is based on established behaviour change counselling methods, including MI and CBT, and incorporates clinical practice change theory. It is designed to improve motivation to eat despite a range of barriers (pain, mucositis, nausea, reduced or no saliva, taste changes and appetite loss), and to provide patients with practical behaviour change strategies. EAT will be delivered by dietitians during their usual consultations. 400 patients with HNC (nasopharynx, hypopharynx, oropharynx, oral cavity or larynx), aged 18+, undergoing RT (>60 Gy) with curative intent, will be recruited from RT departments at five Australian sites. Assessments will be conducted at four time points (first and final week of RT, four and 12 weeks post RT). The primary outcome will be a nutritional status assessment.

INTRODUCTION

Rationale

Malignancies of the upper aerodigestive tract and its connected structures, known collectively as HNCs are the fifth most commonly diagnosed cancers worldwide (1). HNC has a relatively high mortality rate, approaching 50% (2). Malnutrition is a major problem for people with HNC. The prevalence of malnutrition across all patients with cancer in Australia has been reported as between 40% and 80%, with patients with HNC over-represented in this figure (3). The malignancy itself can cause difficulty in eating, fatigue, loss of appetite and weight loss; and treatments for the cancer can compound these problems with mucositis, dry mouth and taste changes (4).

Impact of malnutrition

The consequences of malnutrition in patients with cancer include impaired immune function, reduced vitality and reduced resistance to the disease, which lead to an increase in complications due to side effects of the treatment and increased morbidity (5). Further, the effectiveness of the RT itself is significantly reduced if the patient becomes so malnourished they require a break or early termination of treatment (6). Multiple laboratory and clinical trials have demonstrated that treatment interruption is the strongest predictor of poor RT outcome (7), and malnutrition is one of the most common reasons for treatment to be interrupted (8). Therefore, it is not surprising that poor nutritional status during treatment has been found to be a strong predictor of mortality in HNC (9). Further, a dose effect of malnutrition has been found, with a greater than 20% weight reduction over the course of treatment resulting in a significant increase in toxicity and mortality during RT (10). Given the impact of malnutrition on the health of people with HNC and their response to treatment, it is usual practice for patients to consult regularly with a dietitian throughout the course of their treatment.

Mental illness in HNC

In addition to nutritional difficulties, patients with HNC also exhibit relatively high rates of mental health problems, particularly depression (11). Our recent study found that baseline depression predicted those patients with HNC who were most likely to become malnourished by the end of their treatment (12). Depression was a better predictor than the commonly accepted risk factors for malnutrition: gender, age, presence of a live-in carer, tumour stage, dose of radiation, concurrent chemotherapy or surgery (12). It has also been suggested that the high levels of disfigurement and loss of functioning in HNC may lead to greater levels of anxiety than those found in other cancer populations (13). Furthermore, the risk factors for HNC (smoking and alcohol misuse) (14) may be indicative of premorbid depression (15) in these patients, and have been linked to worse treatment side effects (16-19) and poorer outcomes of RT (20-23). Despite the high prevalence of mental illness among patients with HNC and the implications for treatment, a recent systematic review reported that no studies have evaluated psychological interventions targeting health behaviours among patients with HNC (24).

Compliance problems in HNC

Patient compliance with dietary advice is essential to achieve positive treatment and health outcomes. A systematic review of nutrition advice in patients with HNC receiving RT found that dietetic intervention throughout treatment maintained or improved patients' nutritional status (25). Furthermore, nutritional advice has been found to improve a range of patient outcomes during (26) and after treatment (27), including treatment completion rates, unplanned hospital visits, length of stay and weight loss (28). However, patients with HNC are often non-compliant with dietary advice. For some, having to return to the hospital for dietetic appointments in addition

to their RT can be an impediment; particularly if the appointments are not viewed as a core component of their cancer treatment. In response, dietitians often lack the specific confidence, skills and time to change the dietary behaviours of patients with HNC, especially if those patients have mental health and/or substance use problems and may not see dietetic care as important.

Eating As Treatment

This trial attempts to address the inherent difficulties in intervening with the HNC population including their premorbid mental health, non-engagement and non-compliance with dietary advice. It does this by providing dietitians with training, skills and knowledge to deal with this difficult and often overlooked group. The study builds on previous findings by employing MI (29), a counselling style shown to be effective among other non-compliant patient groups (30) and simple cognitive and behavioural strategies. Dietitians will be trained, supervised and coached in the provision of the intervention known as EAT, guided by an intervention manual (available on request). Dietitians will also receive training in the administration of a brief screening tool for symptoms of depression. In accordance with best practice recommendations, dietitians will be supported to identify patients at risk of psychosocial distress and to work with the HNC team to mobilise appropriate support. A raft of evidence based practice change strategies will also be adopted to overcome systemic and other barriers to clinician compliance, thereby maximising the clinical implementation of EAT.

Objectives

This trial aims to test the effectiveness of the EAT intervention. EAT is a dietitian-delivered intervention to prevent malnutrition in patients with HNC undergoing RT at five Australian hospital sites. The primary objective of the trial is to maintain nutrition

in patients with HNC undergoing RT.

It is hypothesised that patients with HNC receiving the EAT intervention will have lower malnutrition scores, as measured by the Patient-Generated—Subjective Global Assessment (PG-SGA), at post-treatment and follow-up, compared with patients in the control condition (receiving usual care).

Secondary hypotheses are that, relative to control patients, intervention patients will have higher rates of treatment completion, fewer unplanned hospital visits, shorter lengths of stay, lower depression, higher QoL and more quality adjusted life years.

METHODS AND ANALYSIS

Trial design

The present study utilises a stepped-wedge, cluster-randomised controlled design. In a stepped-wedge design, all recruitment sites (hospitals) begin in the control condition and then move to the intervention condition in a randomised order (Figure 1). This design was chosen because the intervention involves training dietitians and changing their practice, a simple, randomised trial would require the dietitians to ignore the intervention principles and skills they have learned when treating control patients, making the likelihood for contamination very high. Therefore, a cluster-randomised design was necessary. A standard, parallel, cluster-randomised trial would require a large number of hospitals that treat high numbers of patients with HNC. The low number of RT departments in Australia treating high numbers of patients with HNC meant that this option was also not possible. A stepped-wedge, cluster-randomised, controlled trial provides the same level of evidence as a standard, parallel, cluster-RCT

(31) using fewer sites, while reducing the potential for contamination.

	Initiation	Step 1	Step 2	Step 3	Step 4	Step 5
Adelaide	Control	Intervention	Intervention	Intervention	Intervention	Intervention
Melbourne	Control	Control	Intervention	Intervention	Intervention	Intervention
Sydney	Control	Control	Control	Intervention	Intervention	Intervention
Perth	Control	Control	Control	Control	Intervention	Intervention
Brisbane	Control	Control	Control	Control	Control	Intervention

Figure 1. Progression of intervention roll-out in a stepped-wedge model

Recruitment

Sites were recruited through the Trans-Tasman Radiation Oncology Group (TROG) who invited members from large RT departments within Australian hospitals to put their sites forward as potential clusters. Participants will be recruited from six of these large RT departments located in Adelaide, South Australia; Melbourne, Victoria; Sydney, New South Wales; Perth, Western Australia; and Brisbane, Queensland. There are two hospitals in Brisbane that share a dietetic department. So, although patients are recruited from two different hospitals, they will be treated as one progression step in the stepped wedge, and move to the intervention period at the same time. This equates to a total of five wedge steps.

Prior to study commencement, the order in which hospitals receive training (thereby the duration of control and intervention periods) was randomised by an independent statistician using a uniform random number generator in STATA. The randomised order was Adelaide, Melbourne, Sydney, Perth and Brisbane.

Participants

Inclusion criteria

Patients eligible for inclusion will meet the following criteria:

• Aged 18 years or older.

• Pathologically confirmed diagnosis of HNC, that is, cancer involving the

    nasopharynx, oropharynx, oral cavity, larynx, or hypopharynx, requiring

    definitive or postoperative RT with curative intent (chemoradiation (including

    neoadjuvant and adjuvant chemotherapy) permitted).

• Regional nodal irradiation included in PTV1 (as a minimum ipsilateral levels II-III),

    and receiving a prescribed dose of at least 60 Gy.

• Available for follow-up for at least six months poststudy initiation.

• Capacity to provide written informed consent.

Exclusion criteria

• Inability to communicate in English.

• Presence of organic brain diseases (impairing ability to complete questionnaires

    satisfactorily).

• Likely insignificant oral or pharyngeal mucositis as a complication of RT treatment

    (patients with T1/T2 glottic carcinoma undergoing small-field RT or T1/T2

    tonsil cancer undergoing unilateral treatment).

Recruitment

Approximately one participant per week per hospital will be expected to be enrolled in the study. It is estimated that at this rate, recruitment will run for approximately 22 months.

Treatment

Control

During the control phase, each hospital will be instructed to deliver treatment as usual, making no changes to any part of their clinical care.

Intervention

Training

When a hospital moves from control to intervention, researchers will travel to the hospital to provide training. This will be delivered in a two-day workshop followed by a day in which a booster training session is delivered, followed by the researchers accompanying dietitians during their usual consultations to help them integrate into their clinical practice what they have learned. The researchers will return two months later to refresh EAT intervention skills, problem-solve clinical concerns, and troubleshoot any practice change issues that may have arisen. During the intervention phase, dietitians will participate in regular supervision with one of the researchers (clinical psychologist, AKB). Where possible, individual supervision via telephone will occur fortnightly for the first two months post-training, and regular written feedback will be provided. Group supervision will be introduced during the two-month 'booster' visit.

Group supervision will then occur monthly, thereafter, via skype/teleconference/videoconference. Supervision will be used to discuss clinical issues, problem-solve, and provide skills-based feedback. Common themes, barriers and solutions discussed during supervision will be distributed (eg, email/discussion board) to participating dietitians across all hospitals.

Eating As Treatment

The intervention is named EAT, to emphasise that maintaining adequate nutrition during RT is an integral part of cancer treatment and not merely an adjunct to survival. In order for patients with HNC to eat, they must overcome significant barriers of pain, oral disfigurement, mucositis, nausea, reduced or no saliva, taste changes and severe loss of appetite, in addition to the premorbid complications of high rates of smoking, alcohol misuse, mental health problems and poor levels of self-care.

The content of the intervention is a distillation of behaviour change strategies of MI and CBT, developed specifically for patients with HNC undergoing RT and targeting behaviours around nutrition. The intervention was successfully piloted by a clinical psychologist (12), and has been refined for delivery by dietitians in the clinical setting, alongside their standard dietetic consultations with patients with HNC. The refined training was piloted with dietitians at the Calvary Mater Newcastle, who found the training acceptable, feasible and useful.

Although the training is standardised, the intervention itself is not highly structured, as it has been demonstrated that MI studies that do not have a structured manual produce almost double the effect size of those that are highly manualised (32). Instead, training in EAT uses simply worded principles to guide the dietitian (Figure 2), reminding them to integrate the skills they have learned in training into their normal clinical practice. The first principle refers to the MI interactional style in which clinicians are empathic, collaborative and elicit motivation for change from the patients themselves (29). This principle refers both to the importance of allowing the patient reinforce their own reasons for change (change talk), as well as avoiding pushing the patient into creating

Figure 2. Principles prompt and conversation guide for Eating As Treatment

arguments not to change (sustain talk). These skills will be used to elicit motivation to change eating behaviour and to help generate concrete behavioural goals (Appendix A11).

There are no specific 'scripts' in EAT. However, there is one specific conversation that dietitians will be trained to hold with patients, referred to as Eat To Live. Using MI skills, dietitians will elicit patients' reasons for having RT. Although patients' reasons

will be many and varied, ultimately, a core reason for undergoing the rigours of radiotherapy will have some element of wanting to live (palliative treatment is an exclusion criterion). We can be confident that this is the case, as they are attending RT every day for five to seven weeks, despite sometimes quite severe side effects. Dietitians then offer an invitation to explain the correlation between malnutrition during radiotherapy and poorer outcomes. It is important that this information is delivered as a description of the HNC population rather than becoming accusatory of the patient's behaviour personally, thus keeping to the first principle. The dietitian then deploys variance by inviting the patient to reflect on their continued attendance at RT and their concurrent nutritional behaviours that may not be enhancing the likelihood of meeting the core goal of living. As always, deploying variance requires a good rapport and genuineness for it not to seem accusatory and confrontational. From this point, the dietitian attempts to convert the motivation elicited into concrete dietary behavioural changes by asking the patient what they feel are the next step.

The remaining three principles in EAT will be operationalised in a nutritional planner that the dietitian and patient work on collaboratively. Together, they generate a weekly grid of nutritional behaviours, such as eating breakfast, conducting oral care of ulcers, or drinking a meal replacement supplement. When the patient is happy with the plan, both they and the dietitian sign it, and the dietitian takes a copy and they agree to review it the following week. The patient then ticks each behaviour as they complete it each day. This process makes the behaviours more likely through self-generation (29), self-monitoring (33), having a concrete meal plan (34), tailoring (35), achievability (36), reinforcement and accountability (37); all of which are CBT strategies that have been successful in nutritional behaviour change trials (38).

Implementation of EAT

The intervention was developed to integrate with the *Evidence Based Practice Guidelines for the Nutritional Management of Adult Patients with Head and Neck Cancer* (39). While EAT is predominately a style of interaction, in order to maximise potential benefit for patients, it requires that (1) patients receive frequent contact with dietitians to enable sufficient exposure to the intervention; (2) ongoing dietitian's use of a validated nutrition assessment tool to enable the dietitian to present a patient's non-compliance with dietetic advice in a standard, objective, but non-confrontational way and that (3) patients at risk of depression be offered psychosocial support to reduce the risk that depressive symptoms do not hinder patient motivation and capacity to engage with dietitians or action nutritional plans agreed with dietitians during consultation. As such, during the intervention phase, sites receive a range of supportive clinical practice change strategies to facilitate the delivery of the EAT intervention in addition to the provision and/or maintenance of clinical practice guidelines recommendations regarding the frequency of dietitian contact during and after RT, the use of a validated nutritional assessment tool to assess and monitor nutritional adequacy of patients, and the screening and referral of patients at risk for psychosocial support. Specifically, the research team will provide sites with the following evidence-based, clinical practice change support strategies.

Box 1 **Best practice clinical guidelines for patients with head and neck cancer**
Best practice clinical guidelines for patients with head and neck cancer recommend:

- ≥125 kJ/kg/day and 1.2 g protein/kg/day
- Use of a validated nutritional assessment tool
- Dietetic consults weekly, then fortnightly
- Screening and referral for distress

Executive support and endorsement

Senior trial investigators will solicit the support and endorsement of executive staff from each site for the implementation of the EAT intervention and dietetic clinical guidelines (40-42). These trial investigators include clinical psychologists, an implementation scientist, and an expert opinion leader in the field of head and neck dietetic care, and author of the *Evidence-Based Practice Guidelines for the Nutritional Management of Adult Patients with Head and Neck Cancer* (39). Specifically, these members of the research team will meet via teleconference with the department head of dietetics and the principal investigator from the RT department at each participating site two weeks prior to training (described below). These executive site staff will be asked to demonstrate leadership and support for the EAT intervention and clinical guidelines, for example, by communicating their support for the clinical practice change and expectations of staff at the training workshops and throughout the intervention phase of the trial. These staff will also be asked to take responsibility for addressing any barriers to change arising at the executive level.

Provision of staff training

The workshop and booster session (described previously) will seek to enhance staff knowledge, skills and attitudes toward the EAT intervention and the best practice dietetic guidelines, and address barriers to such care provision identified in the literature. Specific to depression-screening recommendations, dietitians will be trained in a method used to screen for symptoms of depression using the PHQ-2 (43). The PHQ-2 consists of two key screening items from the larger PHQ-9 and has been shown to have good psychometric properties (ROC AUC=0.084) in a RT outpatients population (44). It asks the participant to rate the frequency of two major depressive episode criteria over the last two weeks from 0 to 3. This provides the clinician with an

indication of whether the patient may be at risk of experiencing clinically significant symptoms of depression. Training will combine didactic and interactive components including opportunities for discussion, role play and facilitator-provided feedback. This approach is consistent with recommendations for effective training that facilitates learning (45-46).

Academic detailing

Clinical psychologists from the research team will attend the RT department dietetic clinics to 'shadow' dietitians for one day following both the two-day training workshop and the booster training session (two months after initial training). The research staff will be guided in this process by the use of a checklist that clearly defines the educational and behavioural objectives of the EAT intervention and clinical guidelines. The clinical psychologists will (1) reinforce the essential messages using active dietitian participation, (2) informally assess intervention implementation, (3) help resolve implementation barriers and assist with the integration of systems changes specific to that clinic to support best practice dietetic intervention, (4) provide advice, feedback, support and positive reinforcement of improved practices to dietitians regarding patient care and (5) set explicit targets and develop an action plan with dietitians (47-49).

Systems and prompts

To facilitate patient attendance for dietetic treatment, services will be encouraged to schedule outpatient appointments adjacent to RT appointments. Integrating dietetic management into RT in this way helps to position dietetic intervention and counselling as an integral part of cancer care for both the patients and the department staff. Dietitians will be asked to schedule patient consultations according to the recommendations of the clinical guidelines (weekly during RT, fortnightly for six weeks post-treatment, and 'as required' thereafter). Dietitians will be asked to record

dietetic consultations in patient medical records. Consistent with recommendations for effective implementation of clinical guidelines into routine practice, the medical records of participating patients will include a coloured printed prompt, placed by research staff, to remind and guide dietitians in the key components of the EAT intervention. The PG-SGA and PHQ-2 will also be included in trial patients' records to facilitate standardised nutrition assessment and depression screening as recommended by the clinical guidelines (50). For services without existing referral pathways for psychosocial support for patients with cancer, the research team will work with the dietitians and radiation oncologist at each site to collaboratively develop a referral policy for those patients screened as at risk for depression.

Performance audit and feedback

Patient medical records and audio recorded patient consultations will be audited regularly by study personnel to assess the provision of the EAT intervention behavioural change techniques and care consistent with the clinical guidelines. Consistent with recommendations for effective feedback and monitoring, feedback regarding site performance data relative to agreed benchmarks will be provided in written and verbal forms at multiple timepoints (48-49). The expert opinion leader in HNC nutritional management and the behavioural scientist from the research team will have regular phone meetings every three to four months with the head of the dietetics departments of the intervention sites to provide information about the current level of care provided by staff, relative to best practice guidelines and the EAT intervention. Reports providing aggregated data will be provided to the head of dietetics at each site prior to these calls at three to four month intervals after training. With permission of the head of dietetics, these reports will also be sent to site dietetic staff. During these calls, the expert opinion leader will review performance feedback using these reports, identify

opportunities for improvement, assist with problem solving, agree on the goals for the next month including performance benchmarks, and set an action plan (48). The head of dietetics at the intervention site will be encouraged to implement strategies to improve care when it is found to be inconsistent with the EAT intervention components.

Additional support and feedback for the intervention will be provided as part of academic detailing, and through ongoing formal and informal supervision, with a clinical psychologist assisting with the implementation, barriers and maintenance of the system change. As part of these regular meetings, audio tapes of dietetic consultations with trial patients will be discussed. Those clinicians not meeting benchmarks will be encouraged to discuss potential impediments with the clinical psychologist during supervision.

Provision of tools and resources

Given identified barriers to implementation of clinical guidelines including lack of information and clinical uncertainty (50-51), services and staff will have access to well presented, user friendly EAT intervention manuals and print resources, nutrition assessment tools, depression-screening procedures and psychosocial referral options that will be provided during training, so as to facilitate discussion and practice (40-41, 52). They will also have access to regular phone and videoconferences with the clinical psychologist and project manager to discuss barriers and solutions to implementation. Barriers to intervention implementation and any necessary resources required for training will be discussed during a teleconference with sites two weeks prior to training.

Treatment verification and delivery

Dietitians will be required to audio-record treatment sessions with participants and to

use a monitoring form to document the number and frequency of their dietetic consultations. A random selection of audio tapes pretraining and post-training, will be reviewed by two independent assessors for fidelity to the EAT manual. Fidelity will be assessed using the Behaviour Change Counselling Index (53-54), a standardised, evidence-based checklist for assessing behaviour change counselling skills. Following the EAT training, additional items will be added to assess the presence of specific components of the EAT intervention.

Assessments

Assessments of primary and secondary outcomes and covariates will be conducted by an independent research officer during the first and last weeks of RT (typically six weeks apart) and follow-up will occur four and 12 weeks after the completion of RT (Table 1). As part of routine treatment, the Common Terminology Criteria for Adverse Events (55), mucositis (oral, pharyngeal and laryngeal) and dysphagia assessments will also be performed by the radiation oncologist.

Primary outcome: Nutritional status

The PG-SGA (56-57) is considered the gold standard in oncology nutrition. The assessment examines known prognostic indicators of nutrition such as weight change, dietary intake, gastrointestinal symptoms, changes in functional capacity, nutritional intake, metabolic stress, subcutaneous fat, muscle wasting, disease and treatment. It consists of a self-report questionnaire and clinical assessment conducted by a member of the study team. Higher scores reflect a higher risk of malnutrition.

Table 1. Schedule of assessment measures

	First week of radiotherapy	Last week of radiotherapy	Four weeks after	Twelve weeks after
Primary outcome				
Nutritional status assessment: PG-SGA	✓	✓	✓	✓
Secondary outcomes				
Depression: PHQ-9	✓	✓	✓	✓
Quality of life: EORTC	✓	✓	✓	✓
Quality adjusted life years: EORTC	✓	✓	✓	✓
Covariates				
Therapeutic alliance: dietitian ARM-5 (clinician)	✓		✓	✓
Therapeutic alliance: client ARM-5 (client)	✓		✓	✓
Nicotine dependence: FTND	✓		✓	✓
Alcohol dependence: AUDIT	✓			
Alcohol use: AUDIT-consumption	✓		✓	✓
Smoking: biochemical validation expired carbon monoxide	✓		✓	✓
Dysphagia: Australian standard of food texture	✓	✓	✓	✓
Chart audit	✓			✓

ARM-5, Agnew Relationship Measure—Five Item Version; AUDIT, The Alcohol Use Disorders Identification Test; EORTC, European Organisation for Research and Treatment of Cancer; FTND, The Fagerstrom Test for Nicotine Dependence; PG-SGA, Patient Generated Subjective Global Assessment; PHQ-9, The Patient Health Questionnaire 9.

Secondary outcomes

Depression: The PHQ-9 (43) is a self-administered nine-item questionnaire that assesses depression. Participants are asked to rate (on a scale of 0–3) the frequency of various MDE criteria over the previous two weeks. It provides two pieces of information; whether the patient is likely to meet criteria for a MDE, and a measure of the severity of the depression from 0 to 27.

Quality of Life: The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) is a psychometrically validated (58) 30-item self-report questionnaire designed to measure quality of life in patients with cancer. The EORTC QLQ-C30 consists of five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea and vomiting), a global health status scale, and six single items assessing the perceived financial impact of the disease and additional symptoms commonly reported by patients with cancer (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea). Scale and individual item scores range 0–100. Higher scores reflect a higher response level—high functional scores indicate a high/healthy level of functioning; higher symptom scores reflecting higher symptomatology/problems; higher scores on individual items reflect stronger endorsement/experience of that item. The EORTC QLQ-C30 can also be used to generate quality adjusted life years for economic analyses (59-60).

Other variables

Therapeutic alliance: This is measured by the Agnew Relationship Measure—Five Item Version—Patient Rated (ARM-5; 61). This short questionnaire has been developed as a mechanism for assessing therapeutic alliance within busy clinical settings (61). The

ARM5 comprises a single 'core alliance' domain consisting of items from the ARM bond, partnership and confidence domains. The ARM5 consists of a series of statements on parallel forms rated by clients and clinicians using a seven-point Likert scale anchored 'strongly disagree', 'moderately disagree', 'slightly disagree', 'neutral', 'slightly agree', 'moderately agree' and 'strongly agree'. Clinicians and clients are asked to rate items 'thinking about today's meeting'. An overall 'core alliance' scale is derived by calculating the mean of the five items, with higher scores reflecting stronger therapeutic alliance.

Nicotine dependence: The FTND (62) is a six-item, reliable and valid self-report questionnaire designed to assess the strength of nicotine dependence. Item scores are summed to produce a total score, with higher scores indicating higher levels of nicotine dependence (0–2=very low; 3–4=low; 5=medium; 6–7=high; 8–10=very high dependence).
Expired CO will provide biochemical verification of smoking status.

The AUDIT (64) is a ten item self-report measure developed by WHO to identify harmful patterns of alcohol use over the preceding one year (including harmful use, hazardous use and dependence). Items are summed to produce a total score, with scores over eight indicating harmful or hazardous alcohol use, as well as possible alcohol dependence. Inspection of individual items can be used to further identify the nature of alcohol-related problems. Scores above zero on items 1–3 can signify risky or hazardous use; on items 4–6 (especially weekly or daily symptoms), scores above zero are indicative of the presence or incipience of alcohol dependence, while endorsement of items 7–10 demonstrates that alcohol-related harm is already occurring (65).

The AUDIT-Consumption (64) consists of the first three items of the AUDIT (frequency of use, typical consumption and frequency of six or more standard drinks), and provides an index of alcohol use. This brief questionnaire is a reliable indicator of heavy drinking and also demonstrates adequate sensitivity and specificity for detecting active alcohol abuse and dependence (64). It will be employed to detect changes in quantity and/or type of alcohol consumed across the 18 weeks of the trial, with reference to a two-month time frame.

Dysphagia: The research officer will conduct a secondary assessment of dysphagia as it relates to nutrition using the Australian Standard of Food Texture. The assessor will record the participant's ability to swallow to a standard level: unmodified (regular), texture A (soft), texture B (minced moist), texture C (smooth pureed), and to drink water without coughing or choking.

Chart review

Outcome and covariate data (Table 2) will also be collected by a member of the study team during chart reviews conducted during the first week of RT and at 12-week follow-up.

Chart audit

A chart audit will also be conducted on those patients who met the three key screening criteria but were not enrolled in the study. A summary of the following variables will be generated to allow for any recruitment or drop-out bias to be controlled for in analysis: standard demographics; tumour site, stage and response; proposed and delivered

concurrent chemotherapy; concurrent surgery; number and frequency of dietetic consults; unplanned hospital visits, length of stay; prescribed and delivered RT dose, fractionation, treatment time and treatment interruption(s); whether a PEG or NGT was used prophylactically, or for alimentation during treatment or post-treatment; and mortality data.

Sample size

The target sample size for this trial will be 400 (approximately 80 participants per recruitment hospital). This sample size calculation was based on a t test using the Harvard Biostatistics Massachusetts General Hospital Biostatistics Power and Sample Size Calculator, providing 80% probability that the study will detect a treatment difference at a two-sided 0.05 significance level with a minimum important difference of two units on the PG-SGA, assuming the SD is seven.

Statistical analysis

The primary outcome of nutritional status as measured by the PG-SGA will be analysed using a Generalised Linear Mixed Model to take account of the repeated measurements on subjects over time (assessment moment). The model will include the cluster-level variables of intervention (pre and post) and hospital. Individual-level variables in the model will be baseline nutritional status as measured by the PG-SGA, calendar time, assessment moment, as well as tumour site and tumour stage. A random effect for individual will be included in the model as well as a random effect for assessment moment, as the variation in PG-SGA is likely to be much greater at the assessment moment during the patient's treatment phase. Finally, an interaction term for intervention by assessment moment will be included in the model to allow the treatment

Table 2. Outcome and covariate data extracted during chart reviews

Week one	Twelve weeks follow-up
Tumour site	Delivered radiotherapy dose, fractionation, start date, finish date and total treatment time
Tumour stage	Treatment interruption
Concurrent chemotherapy	Unplanned hospital visits and length of stay
Concurrent surgery	Tumour response
Proposed RT dose, fractionation and treatment time	Whether PHQ-2 follow-up was documented
Prophylactic PEG/nasogastric tube feeding placement and date inserted	Number and frequency of dietetic consults
Whether PHQ-2 screening was documented	Whether PG-SGA/formal nutritional assessment was documented in the final week of treatment and the score
Whether PG-SGA/formal nutritional assessment was documented in the first week of treatment and the score	Complications with PEG/date of removal of PEG if removed
	Whether a PEG or nasogastric tube feeding was used for alimentation during treatment or post treatment and date inserted and removed
	The dates and dosage of all medications/treatments received as part of another clinical trial

PEG, Percutaneous endoscopic gastrostomy; PG-SGA, Patient Generated Subjective Global Assessment; PHQ-2, The Patient Health Questionnaire 2; RT, radiotherapy.

effect to vary over time.

DISCUSSION

The present study is significant in that it addresses the issue of malnutrition during RT, a major risk factor for morbidity and mortality in patients with HNC. Although mucosal cancers of the head and neck have traditionally accounted for approximately 3% (2) of all cancer diagnoses, the frequency of this diagnosis has increased exponentially in recent years. RT plays a major role in the management of these patients, often in association with surgery or chemotherapy. This is the first study to evaluate a dietitian-delivered behaviour change intervention (EAT) based on MI and CBT to maintain or improve nutritional status among patients with HNC. The results of the proposed trial are expected to make a significant contribution to dietetic clinical practice, the training of future oncology dietitians, and ultimately, to reducing the mortality of patients with HNC.

Importantly, this study brings together existing research, clinical experience and promising pilot data collected by the research team. It is a collaboration between investigators internationally recognised in their respective fields of oncology, psychiatry, dietetics, health behaviour and systems change, working towards better outcomes for this challenging and often overlooked cancer population.

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PAPER FIVE: EFFECTIVENESS OF CLINICAL PRACTICE CHANGE STRATEGIES IN IMPROVING DIETITIAN CARE FOR HEAD AND NECK CANCER PATIENTS ACCORDING TO EVIDENCE BASED CLINICAL GUIDELINES: A STEPPED WEDGE RANDOMISED CONTROLLED TRIAL

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Associated Appendices:

PAPER FIVE: Effectiveness of clinical practice change strategies in improving dietitians care for head and neck cancer patients according to evidence based clinical guidelines: A stepped-wedge randomised controlled trial

ABSTRACT

Background: Best practice guidelines make a number of recommendations regarding dietitian management of HNC patients. Randomised trials assessing the effectiveness of clinical practice change strategies for improving the nutritional management of HNC patients have not previously been conducted.

Objective: The purpose of this study was to evaluate the effect of practice change strategies on improving the implementation of best-practice guideline recommendations for the nutritional management of HNC patients.

Design: Four Australian RT departments participated in a stepped-wedge RCT. Baseline data were collected across all sites simultaneously and the intervention was then introduced to each site sequentially, in a randomly determined order. During the intervention phase, sites received a range of supportive clinical practice change strategies to facilitate dietitian adherence to clinical practice guidelines. In order to assess the associated practice change by dietitian staff, we evaluated the change in implementation of six guideline recommendations for dietitians from control to intervention periods.

Results: Adherence to the clinical practice guidelines during the control period was generally very low. The clinical practice change strategies significantly improved the odds of provision of four of the six guideline recommendations.

Conclusions: The study found the intervention significantly enhanced dietitian provision of recommended care for HNC patients during the intervention period. This finding holds clinical importance for clinician and health service effective implementation of guideline recommendations as well as HNC patient treatment outcomes.

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INTRODUCTION

Background

Malnutrition is common in HNC, being present in approximately 30-50% of such patients (1, 2). The malignancy and its treatments can contribute to malnutrition through problems with eating, fatigue, decreased appetite and weight loss (3). Malnutrition is of particular concern for cancer patients given its association with increased risk of morbidity (3) and overall mortality (1). Similarly psychological distress can affect patient functioning, capacity to cope, treatment compliance, QoL and survival (4, 5) and depression increases the risk of malnutrition (6).

Given the importance of nutrition management, the National Institute for Health and Clinical Excellence guidelines recommend the inclusion of an oncology dietitian as a core member of a multidisciplinary team responsible for the care and management of HNC patients (7). To improve treatment outcomes, best practice guidelines make a number of recommendations regarding dietitian management of HNC patients including: weekly consultation with a dietitian during RT, fortnightly consultations for at least six weeks post treatment; use of a validated nutrition assessment tool to assess nutritional status; and monitoring weight, intake and nutritional status during and post (chemo) RT (8). Clinical practice guidelines also recommend patients are screened for distress and indicated patients provided with psychosocial support (8-10). Despite such guidelines, research suggests that many patients do not receive care consistent with best practice guidelines. (11, 12).

Unless clinical practice guidelines are implemented, their potential benefits in improving patient outcomes will not be realized. Systematic reviews suggest that guideline

complexity, a lack of awareness of guideline recommendations, limited time, a lack of organizational support and resources impede the alignment of clinical care with guideline recommendations (13-20). To our knowledge, randomised trials assessing the effectiveness of clinical practice change strategies in overcoming such barriers and improving the nutritional management of HNC patients have not previously been conducted. Systematic reviews of clinical research more broadly, however, suggests multi-strategic clinical practice change intervention can improve guideline adherence (21). The aim of this trial was to assess the impact of such practice change strategies in improving dietitian implementation of best-practice guideline recommendations for the nutritional management of HNC patients.

METHODS AND ANALYSIS

Context

This study was conducted as part of a multi-centre trial of a dietitian delivered health behavioural counselling intervention, EAT. Full details of the EAT trial have been described elsewhere (22). Briefly, EAT tested an intervention incorporating MI and CBT strategies in reducing malnutrition in patients with HNC undergoing RT.

The EAT intervention was also developed to align with six clinical practice guideline recommendations (8). The specific care provisions based on guideline recommendations that were targeted were:

1. Patient should be seen weekly by a dietitian during RT;

2. Patient should receive minimum fortnightly follow up by a dietitian for at least six weeks post treatment;

3. Nutritional status should be assessed using a validated nutrition assessment tool PG-SGA;

4. Weight, intake and nutritional status should be monitored during and post (chemo) RT;

5. Patients should be screened for depression using the PHQ-2 in Week One of RT;

6. Patients that screen positive (score of ≥3 on the PHQ-2) during Week One of RT should be offered referral for further assessment/and or psychosocial supports.

The EAT intervention was aligned with these guideline recommendations in order to ensure sufficient exposure of patients to the dietitian delivered intervention, the inclusion of behavioural monitoring strategies and the provision of appropriate support due to the link between depression and malnutrition as well as other negative patient outcomes in this population (6, 23). Clinical practice change strategies were implemented during the intervention phase at participating sites to improve adherence to the guideline recommendations relevant to the intervention. This provided an opportunity to conduct a nested study of the implementation of clinical guideline recommendations in RT departments around Australia.

The study protocol and methods were prospectively registered ACTRN12613000320752. Ethics approval from all relevant bodies was granted.

Study design

The study employed a multi-site, stepped-wedge RCT design (22). The stepped wedge RCT design reduced the potential for contamination between sites. Trial sites were RT departments located within major metropolitan Australian hospitals. Consistent with the conventional complete stepped-wedge design, control period data were collected across

all sites simultaneously (24). The intervention was then introduced to each site

sequentially. The order in which the intervention was introduced to sites was randomly

determined. The study design is described in Figure 1.

	Initiation	Step 1	Step 2	Step 3	Step 4	Step 5
Site 1	Control	Intervention	Intervention	Intervention	Intervention	Intervention
Site 2	Control	Control	Intervention	Intervention	Intervention	Intervention
Site 3	Control	Control	Control	Intervention	Intervention	Intervention
Site 4	Control	Control	Control	Control	Intervention	Intervention
Site 5*	Control	Control	Control	Control	Control	Intervention

*Two hospitals

Figure 1. Stepped-wedge, cluster randomised trial design

Participants and recruitment

The study was presented to the TROG at the 2012 Meeting and sites interested in

participating were encouraged to contact the research team. Written information about

the study was also disseminated by TROG to members from large RT departments

within Australian hospitals with an invitation to contact the research team regarding

participation. Six dietetic departments were recruited.

Patient consent was sought to enable collection of data regarding patient receipt of care

consistent with guideline recommendations during control and intervention periods

(Appendix A2). HNC patients who were scheduled for RT at each site were screened

for eligibility. Sites generated a list of patients who met the eligibility criteria using

treatment planning software, multi-disciplinary team meetings and/or clinician referrals.

Eligible patients were those who were scheduled to undergo definitive or postoperative

RT, were 18 years or older and had one or more of the following cancer diagnoses:

nasopharynx, oropharynx, oral cavity, larynx, hypopharynx and were receiving care

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from an oncology dietitian at a participating RT department. Eligible patients were approached with information about the study (by their radiation oncologist and/or an independent data manager) and were invited to participate.

Randomisation and blinding

The order in which the intervention was introduced to RT departments was randomly allocated by an independent statistician using a uniform random number generator in STATA (Statacorp, College station, TX). All clinical dietitians providing oncology services to HNC patients (participating in the EAT study) during the intervention phase were exposed to the clinical practice change intervention.

Due to the nature of the study design it was not possible to blind RT departments, dietitians or outcome assessors to control and intervention period allocation. However, patients were blind to condition.

Strategies to implement clinical practice guideline recommendations

Full description of the implementation strategies are described in the protocol paper. During the intervention phase, sites received a range of supportive clinical practice change strategies to facilitate the delivery of the EAT intervention in addition to the provision and/or maintenance of clinical practice guidelines recommendations. This included recommendations regarding the frequency of dietitian contact during and after RT, the use of a validated nutritional assessment tool to assess and monitor nutritional adequacy of patients, and the screening and referral of patients at risk for psychosocial support. The implementation support strategies were often integrated into strategies or processes to gain support for the trial and improve fidelity of delivery of the behavioural

counselling intervention by dietitians more broadly. Specifically, the research team

provided sites with the following evidence-based, clinical practice change support

strategies (25-34).

1. Executive support and endorsement

Senior trial investigators solicited the support and endorsement of executive staff from

each site for implementation of the intervention and recommendations based on clinical

guidelines (25-27). Specifically, members of the research team met with the department

head of dietetics and senior staff from the RT department at each participating site two

weeks prior to training (Appendix A12, A13). These executive site staff were asked to

demonstrate leadership and support for the EAT intervention and adherence to clinical

guidelines, for example, by communicating their support for clinical practice change in

line with guidelines and expectations of staff at the training workshops and throughout

the intervention phase of the trial.

2. Provision of staff training

RT department oncology dietitians received training over the course of a two day

workshop conducted by the research team. The purpose of the training was to enhance

staff knowledge, skills and attitudes toward the behaviour change intervention elements

and to best practice dietetic guidelines, address barriers to such care provision and to

familiarise themselves with resources and instruments. Dietitians were trained in the

administration of a brief screening tool for symptoms of depression; the PHQ-2 (28)

and the PG-SGA (35, 36) to assess the nutritional adequacy of patients, and consistent

with guideline recommendations were asked to screen all patients using such tools.

Approximately two months after the initial workshop a booster training session was

conducted to troubleshoot any issues that may have arisen with implementation of the

behaviour change intervention or practice guideline recommendations (Appendix A15).

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3. Academic detailing

Clinical psychologists from the research team attended the RT department dietetic clinics to 'shadow' dietitians for one day following both the two-day training workshop and the booster training session (two months after initial training). In addition to providing feedback on intervention delivery and behavioural counselling proficiency, the clinical psychologists monitored adherence to guideline recommendations, provided advice, feedback and support to resolve implementation barriers including systems changes to facilitate regular patient appointments (29-31) (Appendix A14).

4. Systems and prompts

To facilitate patient attendance for dietetic treatment, services were encouraged to amend patient booking systems to schedule outpatient appointments adjacent to RT appointments and according to the recommendations of the clinical guidelines (weekly during radiotherapy, fortnightly for six weeks post-treatment, and 'as required' thereafter). Medical records of participating patients included coloured printed prompts (PG-SGA and PHQ-2), placed by research staff, to prompt standardised nutrition assessment and depression screening as recommended by the clinical guidelines. For services without existing referral pathways for psychosocial support for patients with cancer, the research team worked with the dietitians and radiation oncologists at each site to collaboratively develop a referral policy for those patients screened as at risk for depression.

5. Performance audit and feedback

Patient medical records and audio recorded patient consultations were audited regularly by study personnel to assess compliance with key components of the behavioural counselling intervention, as well as the provision of care consistent with the clinical guidelines. Feedback on site performance relative to agreed benchmarks was provided

in written reports and during telephone contacts every three–four months to the head of

the dietetics departments by an expert senior dietitian and behavioural scientist from the

research team (30) (Appendix A16, A17). Advice and support to resolve

implementation barriers including systems changes was also provided during these

telephone contact sessions (29-31).

6. Provision of tools and resources

Given identified barriers to implementation of clinical guidelines including lack of

information and clinical uncertainty (33, 34), services and staff had access to nutrition

assessment and depression-screening tools that were provided during training, so as to

facilitate discussion and practice (25, 26, 32).

Control

During the control phase, each hospital was instructed to deliver treatment as usual.

Outcomes and data collection

Patient characteristics

As part of the assessment battery of the trial, patients were asked to report their: gender,

age, country of birth, ATSI status, marital status, education and employment status. The

data manager at each site completed pen and paper clinical research forms with patients

to collect this demographic information at baseline (during week one of RT).

Outcomes: Implementation of clinical practice guideline recommendations by

oncology dietitians

The primary outcomes in this report were the proportion of patients receiving dietetic

care consistent with each of the six clinical practice guideline recommendations. Chart

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reviews of patient medical records from the dietitian clinical consultations were conducted by data managers at each site during the first week of RT and at 12-week post-RT. Implementation of clinical practice guidelines were assessed by the research team using the chart review data. The six implementation outcomes based on dietetic clinical guideline recommendations were:

1. Receipt of weekly consultation with the dietitian during RT. (A dietetic consultation was required for at least each eight day interval throughout RT).

2. Fortnightly appointments with the dietitian for six weeks post treatment. (At least three dietetic consultations at 8 day intervals within 42 days of the end of RT

3. Use of a validated nutrition assessment tool (PG-SGA) by the dietitian to assess nutritional status. (Use of PG-SGA during Week One of RT).

4. Monitor weight, intake and nutritional status during and post RT. (Use of PG-SGA at least once during or after RT in addition to Week One of RT).

5. Patients should be screened for depression using the PHQ-2 in Week One of RT.

6. Patients that screen positive (score of ≥3 on the PHQ-2) during Week One of RT should be offered referral for further assessment/and or psychosocial supports.

Delivery of intervention strategies

Project records were used to determine the delivery of the practice change strategies to sites.

Helpfulness of practice change strategies

During booster training (approximately two months after the initial workshop during the intervention period) all dietetic staff at the initial workshop were asked to complete a questionnaire regarding their attitudes toward the helpfulness of the practice change strategies that supported implementation of the EAT intervention and care according to

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best practice guidelines. Dietitians were asked to rate the strategies on a Likert scale with five responses: very unhelpful, unhelpful, neither helpful/unhelpful, helpful, very helpful.

Sample size

The target sample size of 400 patients was based on the primary outcome (change in nutrition score) of the EAT intervention trial. For the practice change outcomes, this sample size was sufficient to detect an absolute increase in the implementation of clinical practice guideline recommendations of approximately 14% assuming a conservative implementation rate in the control phase of 50%, with 80% power and an alpha of 0.05. Such an effect size is consistent with improvements in clinical practice following clinical practice change interventions of similar intensity (37-39).

Statistical analysis

All analyses were conducted in SAS v9.4 (SAS Institute, Cary, North Carolina, USA) statistical software. Descriptive statistics were used to summarise the characteristics of the study sample. The impact of the strategies in improving implementation of each of the six clinical practice recommendations was assessed under an intention to treat framework, using six logistic regression models, including fixed effects for study stage (intervention or control phase) and study site (hospital). Penalised maximum likelihood estimation were used, due to quasi-complete separation of data and effect sizes were reported as odds ratios and 95% confidence intervals. Complete case analysis was performed, due to very low missing data rates. Statistical analyses were two-tailed with a significance level of 0.05.

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The dietetics department in one site serviced two hospitals. Although patients were recruited from two different hospitals, they were treated as one progression step in the stepped wedge study design and moved to the intervention period at the same time (Figure 1).

RESULTS

Recruitment and participant characteristics

Recruitment began in June 2013 and ended in December 2015, with follow-up finishing May 2016. Of the 852 patients identified as eligible, 516 were approached with information about the study and 313 (61%) of these patients were enrolled in the study (Figure 2). Four patients were later withdrawn due to late recognition of ineligibility. Of the 152 patients allocated to the control condition, 151 (99%) completed follow-up measures. Of the 157 patients allocated to the intervention condition, 156 (97%) completed follow-up measures. Patient characteristics are described in Table 1. The mean age was 58 (SD 10), most were male and just over half were married. Sixty-percent of the patients were employed full time or part time in the past year. Fifty-six percent had cancer of the oropharynx, 22% had cancer of the oral cavity, 9% had cancer of the larynx, 8% had cancer of the nasopharynx, 4% had cancer of the hypopharynx and 2% had an unknown primary. Most had stage IV (65%) cancer, 19% and 13% had stage III and II respectively.

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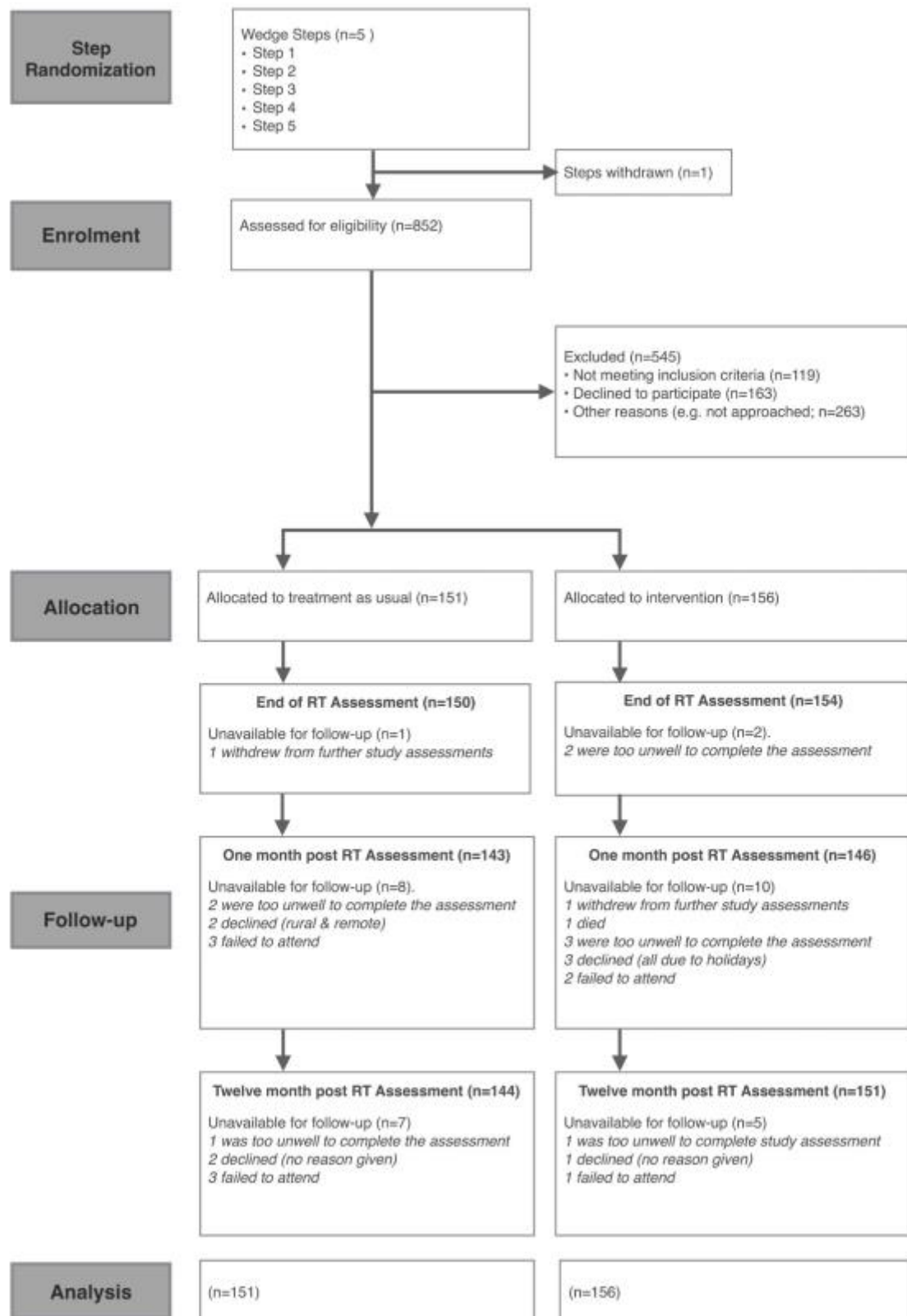
Figure 2. Flow of participants through the trial

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Table 1. Characteristics of sites and patients

Variable	Statistic/class	Control (n = 151)	Intervention (n – 156)
Clinic characteristics			
Number of dietitians		11	18
Patient demographics			
Age (in years)	mean (SD)	58 (10)	58 (11)
Sex	Male	126 (83%)	118 (76%)
Country of birth	Australia	100 (66%)	98 (62%)
	UK & Ireland	13 (9%)	25 (16%)
	Other	38 (25%)	33 (21%)
Speak language other than English at home	Yes	11 (7%)	11 (7%)
Marital status	Married/de facto	102 (68%)	91 (59%)
	Widowed	4 (3%)	8 (5%)
	Separated/Divorced	28 (19%)	29 (19%)
	Single/Never married	17 (11%)	23 (15%)
Education	4 years of high school or less	54 (49%)	58 (40%)
	6 years of high school/TAFE	65 (50%)	63 (41%)
	University	31 (21%)	35 (22%)
	Other	1 (<1%)	
Employment	Full-time or part-time employment	87 (58%)	86 (55%)
	Home duties, studying, volunteer, casual, unemployed, other	23 (15%)	30 (19%)
	Retired	41 (27%)	40 (26%)
Tumour site	Nasopharynx	12 (8%)	11 (7%)
	Oropharynx	83 (55%)	88 (56%)
	Oral cavity	30 (20%)	36 (23%)
	Larynx	14 (9%)	15 (10%)
	Hypopharynx	9 (6%)	2 (1%)
	Unknown primary	3 (2%)	4 (3%)
Tumour Stage	1	6 (4%)	6 (4%)
	2	22 (15%)	17 (11%)
	3	25 (17%)	32 (20%)
	4	98 (65%)	101 (65%)
Centre	Site 1	7 (5%)	16 (10%)
	Site 2	30 (20%)	70 (45%)
	Site 3	46 (31%)	37 (24%)
	Site 4	68 (45%)	33 (21%)

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Outcomes

Guideline implementation

Table 2 reports descriptive and inferential statistics representing improvements in the provision of care consistent with each of the measures of clinical practice guideline recommendations. For each guideline, the percentage of patients that received care according to the guideline recommendation is shown for both Control and Intervention periods. Also shown are odds ratios representing the within-site odds of guideline implementation during the intervention versus control period. The clinical practice change strategy significantly improved the odds of implementation of four of the six guideline recommendations ($p<0.05$). The greatest improvements were found for patient screening for depression (OR=349; 95% CI: 69, 1756; $p<0.0001$). Other guidelines showing improved implementation had estimated odds ratios ranging from 1.84 (weekly contact with dietician) to 11 (monitor weight, intake and nutritional status). Note that while statistical significance was not achieved for distress referral, there was an increase from 0% in the control period to 42.1% in the intervention period ($p=0.0547$). The absence of events during the control period necessitated the use of the less powerful penalized maximum likelihood parameter estimation method.

Helpfulness of practice change strategies

The staff booster questionnaire was completed by eight dietitians. The majority of responses indicated that the implementation strategies were seen as helpful/very helpful by the dietitians (Table 3).

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Table 2 Results of logistic regression models testing for intervention effects on guideline implementation

Guideline	Intervention %	Control %	OR	Lower 95% CL	Upper 95% CL	P-value
Dietitian contact weekly during RT	71.5	63.5	1.84	1.05	3.23	0.0339
Dietitian contact fortnightly for 6 weeks post RT	47.7	48.6	1.08	0.65	1.77	0.7686
Nutritional assessment at Week 1 of RT	89.7	69.1	4.30	2.01	9.19	0.0002
Monitor weight, intake and nutritional status during and post RT	88.8	56.7	11.00	4.74	25.54	<.0001
Depression screening at Week 1 of RT	81.3	0.7	348.82	69.31	1755.62	<.0001
Depression referral at Week 1 of RT	42.1	0.0	37.70	0.93	1530	0.0537

Intervention and control % columns show the percentage of patients that received care according each guideline during the intervention and control periods.

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Table 3 Distribution of dietitian attitudes toward helpfulness of the practice change strategies (*n* = 8)

Questionnaire item	Very unhelpful (n)	Unhelpful (n)	Neither helpful nor unhelpful (n)	Helpful (n)	Very helpful (n)
Staff visits					
The information provided by program staff during their visit to the clinic				3	5
Feedback reports					
The information provided in the feedback reports from the program staff				4	4
Resources					
The prompts for key workshop principles and strategies (e.g. stickers, mugs)				4	4
The PHQ-2 sticker			1	5	2
The medical record prompts relating to best practice clinical guidelines[1]			1	2	4
The depression referral policy developed in collaboration with your team[1]				7	
Supervision					
Meeting with the program clinical psychologist				1	7
Receiving feedback on audio recordings				2	6
Scheduling					
Changing the scheduling of dietetic consultations (i.e. to occur on the same day as radiotherapy appointments)[2]				1	3

[1] n = 1 missing; [2] n = 3 already occurring at site;

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DISCUSSION

This was the first randomised trial to evaluate the impact of a multi-strategic practice change intervention in improving the implementation of best-practice guideline recommendations for the nutritional management of HNC patients by dietitians. The study found the intervention significantly enhanced implementation of guideline recommended care during the intervention period. The findings of our study demonstrate that practice change in this setting is possible if clinicians and health services are adequately supported to achieve guideline implementation and have important implications for health services interested in optimizing the care provided to HNC patients to improve their treatment outcomes and prognosis.

The effects of the intervention in improving the provision of best practice care to patients was larger than trials in other clinical settings. For example, a Cochrane review of tailored interventions to overcome barriers to change including 26 trials reported an increase in the odds of recommended care provision by clinicians of about 50% (OR 1.54, CI 1.16 to 2.01) (40). Five of the six measures of care provision reported in this setting reported greater effect sizes. Similarly, a review by Grimshaw on guideline dissemination and implementation strategies found a median absolute increase in the improvement in measures of recommended clinical practice by clinicians was 10% (41). The median absolute improvement reported in this trial was 26% (-1% - 81%). Such findings suggest that the intervention overcame many of the barriers to the provision of care consistent with guidelines. The practice change intervention described in this trial, therefore, provides one model to support clinicians to improve the nutritional management of HNC patients.

The intervention, however, was not effective in increasing the provision of fortnightly appointments with the dietitian for six weeks post treatment. Anecdotally, funding constraints in many sites limited the availability of staff to support such frequent dietetic contact. Similarly, patients often report time and logistical difficulty in attending regular clinical consultations (42). Identifying more cost efficient models to provide care to patients that accommodate such barriers to frequent dietetic patient contact post-treatment may be required. For example, reducing the time of clinical consultation may increase the number of patients staff are able to provide care to. Similarly, providing telephone support to patients who are unable to attend clinical consultations in person may improve the likelihood that such patients receive frequent dietetic care post treatment. Such models of care should be the subjects of future scientific inquiry.

The trial has a number of strengths including a sample sufficient to detect small but meaningful improvements in clinical practices, the use of random assignment and high participation and retention rates. Nonetheless, a number of limitations of the study should be considered when interpreting trial findings. Site staff (dietitians, data managers) were not blind to participant allocation, which may have introduced bias into dietitian documentation of the provision of guideline recommendations and data manager chart reviews of patient medical records. Further, whilst audio-recoding may represent the gold standard in assessing delivery of care during clinical consultations, this was not feasible due to the scale of the intervention and outcomes measured. Nonetheless, record audits have been found to be a valid measure of care provision, and in this study, for two guideline recommendations (distress screening at Week 1 of RT and distress referral at Week 1 of RT) record audits corresponded closely with audio recordings in a sample of patients' consultations.

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The findings of this research have important implications for the provision of care according to best practice guidelines for HNC patients. Given the efficacy of the practice change strategies to improve oncology dietitian provision of care according to evidence based guidelines for HNC patients, their implementation in other sites providing care to cancer patients is warranted.

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SMOKING CESSATION CARE FOR PATIENTS WITH HEAD AND NECK CANCER

PAPER SIX

INTRODUCTION TO PAPER SIX

Paper Five described the findings of a multi-component clinical practice change strategy to increase the implementation of evidence based guideline recommendations and consequently improve HNC patient care in four hospitals in Australia. The study was successful in significantly improving four of the six recommendations targeted, including routine distress screening by oncology dietitians. Given the complex nature of the etiology, unique challenges facing patients and multifaceted management of HNC patients, the next step in this body of work is to address further complicating factors; tobacco smoking and alcohol use. Given the strength of evidence for the negative effects that smoking has on the development, recurrence and treatment of HNC, coupled with the paucity of evidence based interventions to addressing tobacco smoking in this population, this health risk behaviour warrants significant attention. Paper Six represents this next step towards improving HNC patient care.

PAPER SIX: SMOKING CESSATION CARE AMONG PATIENTS

WITH HEAD AND NECK CANCER: A SYSTEMATIC REVIEW

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Associated Appendices:

Appendix A8 Quality assessment tool for quantitative studies

        A9 Quality assessment tool for quantitative studies dictionary

        A18 PRISMA checklist for Paper Six

        A19 PROSPERO registration for Paper Six

        A20 Search strategy for Paper Six

        A21 Paper Six – Published Manuscript

PAPER SIX: Smoking cessation care among patients with head and neck cancer: A systematic review

ABSTRACT

Introduction

To examine the effectiveness of smoking cessation interventions in improving cessation rates and smoking related behaviour in HNC patients.

Methods and analysis

A systematic review of randomised and non-randomised controlled trials was conducted. We searched the following data sources: CENTRAL in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL up to February 2016. A search of reference lists of included studies and Google Scholar (first 200 citations published online between 2000 and February 2016) was also undertaken. The methodological quality of included studies was assessed using the EPHPP. Two study authors independently screened and extracted data with disagreements resolved via consensus.

Results

Of 5167 studies identified, three were eligible and included in the review. Trial designs of included studies were two randomised and one non-randomised controlled trial. Two studies received a weak methodological rating and one received a moderate methodological rating. The trials examine the impact of the following interventions: (i) nurse delivered CBT via telephone and accompanied by a workbook, combined with pharmacotherapy; (ii) nurse and physician brief advice to quit and information booklets combined with pharmacotherapy; and (iii) surgeon delivered enhanced advice to quit smoking augmented by booster sessions. Only the trial of nurse delivered CBT and pharmacotherapy reported significant increases in smoking cessation rates. One study measured quit attempts and the other assessed consumption of cigarettes per day and

readiness to change. There was no significant improvement in quit attempts or cigarettes smoked per day among patients in the intervention groups, relative to control.

Conclusions

There are very few studies evaluating the effectiveness of smoking cessation interventions that report results specific to the HNC population. The three trials identified reported equivocal findings. Extended CBT counselling coupled with pharmacotherapy may be effective.

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INTRODUCTION

Background

Tobacco use is a key risk factor for HNC (1) with more than 75% of these cancers attributable to the combination of tobacco and alcohol use (2). HPV is another common cause of head and neck cancer and smoking in this group while not causative has been shown to influence prognosis significantly (3). At least one third of patients with HNC continue to smoke after diagnosis (4-6). Continued smoking increases risk for other smoking related diseases, second primary tumours (7), disease recurrence (8) and reduced treatment efficacy, increases toxicity and side effects from RT (5, 9) and negatively affects overall survival (5). Approximately 10-12% of HNC patients develop a new cancer in the head and neck region within 2 to 3 years after the first cancer diagnosis (10).

In addition to the diverse health benefits of permanent smoking cessation, quitting can have more specific benefits to patients with a cancer diagnosis. A number of studies have reported improvements in the prognosis of patients with a cancer diagnosis following smoking cessation (5, 8, 11, 12). For example, quitting smoking among patients with locally advanced HNC has been associated with a two-fold increase in complete response to RT (5). Abstinence from smoking in cancer patients has also been associated with less pain, higher quality of life scores and better performance status (13). Furthermore, smoking abstinence following diagnosis reduces morbidity and mortality (5, 14), particularly among those with smoking related cancers such as HNC and those diagnosed with a curable disease (15).

Systematic reviews of smoking cessation interventions in the general oncology

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population have found that high intensity, multicomponent interventions that include a combination of pharmacological and behavioural approaches are effective in improving cessation rates (16, 17). However, no reviews of the effectiveness of smoking cessation interventions for HNC patients exist. Patients with varying types of cancer have been found to respond differently to cessation treatment depending on the perceived relevance of patient tobacco use to the onset or recovery from cancer (18). Further, among HNC patients, the location of the malignancy and treatment can cause difficulty in eating, fatigue, mucositis, dry mouth and taste changes (19) that may uniquely influence patient receptivity to some pharmacotherapy interventions such as nicotine gum and require a tailored approach to cessation treatment. In addition to smoking, alcohol use is a key risk factor for HNC and a substantial proportion continue to drink alcohol, with approximately 16% continuing to drink at hazardous levels after diagnosis (4, 20). Patients with HNC also exhibit relatively high rates of mental health problems, particularly depression (21). Smoking, alcohol misuse and depressive symptoms tend to cluster and their relationship is complex (22). Patients may drink alcohol or smoke in an attempt to "self-medicate" depressive symptoms (23). Also, depression is associated with cravings for alcohol and nicotine (24). Such comorbidities present further obstacles to smoking cessation in this population (26) and therefore may warrant tailored treatment. Furthermore, research in this particular cancer population has characterised HNC patients as a particularly vulnerable group, with many living alone and having a limited social network (27). These factors may also necessitate extra support for HNC patients to quit smoking.

Given the importance of ceasing tobacco use among HNC patients and the lack of guidance from previous systematic reviews regarding effective cessation treatment

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among this group, the primary aim of this review is to examine the effectiveness of smoking cessation interventions on smoking cessation rates in adult HNC patients.

METHODS AND ANALYSIS

This systematic review was performed in accordance with a predetermined protocol and is reported consistent with the PRISMA statement (28) (Appendix A18). The review was prospectively registered with PROSPERO (CRD42016016421) (Appendix A19).

Eligibility criteria

Study characteristics

Types of studies

Studies with the following study designs were considered for inclusion:

- RCTs, including cluster RCTs;

- Staggered enrolment trials or stepped-wedged trials;

- Quasi-randomised trials;

- Quasi-experimental trials with comparison/control groups, including non-randomised pre–post (before–after) trials with one or more intervention and control groups, time-series/interrupted time-series trials (including multiple baseline trials) with independent control groups, preference trials and regression discontinuity trials;

- Natural experiment studies that have a comparison group.

Trials without parallel comparison or control groups were excluded. There was no restriction based on length of follow-up or the year of publication. Studies were limited to those published in English in peer-reviewed scientific journals. Comparison groups

for included trials could include no intervention controls, 'usual' practice or alternative interventions.

Participants

Participants of included studies were adults diagnosed with HNC (including cancers of the Nasopharynx, oropharynx, oral cavity, larynx and hypopharynx) and current smokers or those who had recently quit, due to the potential for relapse. There were no restrictions on type (e.g. RT, surgery, chemotherapy) or stage (e.g. pre, during, post) of treatment. Studies that examined a heterogeneous group of cancer patients but did not report results specific to a HNC sub-group were excluded. Studies which examined smoking cessation for carers of patients with HNC were excluded.

Types of interventions

Interventions that aimed to improve the smoking cessation outcomes of patients with HNC in which part of the intervention was conducted in a health care setting (e.g. clinics and hospitals) were included. Interventions could include psychosocial and behavioural (such as counselling, brief advice, referral, web-based information and behavioural support) and/or pharmacological components (medication, nicotine replacement therapy; NRT). Interventions targeting improvement of delivery of smoking cessation services were included only when data for changes in smoking outcomes of HNC patients were also reported. Studies that reported on population-level public health interventions (such as mass media campaigns, taxation and restrictions on tobacco advertising) were excluded.

Outcomes

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Primary outcome:

1. To be included trials needed to report a measure of smoking cessation. This could include point prevalence or continuous abstinence, or current smoking status. Smoking cessation could be assessed via self-report (e.g. interviews, questionnaires and surveys) or biochemical measures (e.g. CO or cotinine assessment).

Secondary outcomes:

1. While not an inclusion criterion, we extracted any additional measures of smoking behaviour reported in trials as a study outcome including consumption of cigarettes per day, level of nicotine dependence, quit attempts and stage of change. Such data may be obtained via self-report (e.g. interviews, questionnaires and surveys) or other methods.

Information sources

Electronic databases

The following electronic databases were searched for potentially eligible studies published up to February 2016; CENTRAL in the Cochrane Library, MEDLINE (from 1946), EMBASE (from 1947), PsycINFO (from 1806) and CINAHL (from 1937). The MEDLINE search strategy (Appendix A20) was adapted for other databases and included filters used in other systematic reviews for population (head and neck cancer patients) and based on the Cochrane Tobacco Addiction Group standard review terms for health behaviour (smoking cessation).

Other sources

Studies were also obtained from the following sources:

- Reference lists of included studies;

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- A search of Google Scholar (published online between 2000 and February 2016 – the first 200 citations were examined)

Study selection

The titles and abstracts retrieved by electronic searches were exported to reference management software (Endnote version X6) to remove duplicates. References were exported to the online software tool Covidence for screening. One reviewer (UM) performed title and abstract screening. Two reviewers (KM and UM) then independently performed full-text screening, data extraction and quality assessment. Reasons for exclusion of full texts were recorded and documented in Figure 1. Any discrepancies were resolved by discussion between the reviewers.

Data extraction

Two review authors (KM and UM) independently extracted data from the included trials using a pre-piloted data extraction form that was developed based on recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions* (29). Discrepancies between reviewers regarding data extraction were resolved by discussion and consensus. The characteristics of each study were extracted, including: study design, setting, country, participants, gender, age, intervention characteristics and outcomes.

Assessment of methodological quality

Studies included in the review were assessed for methodological quality using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP) for

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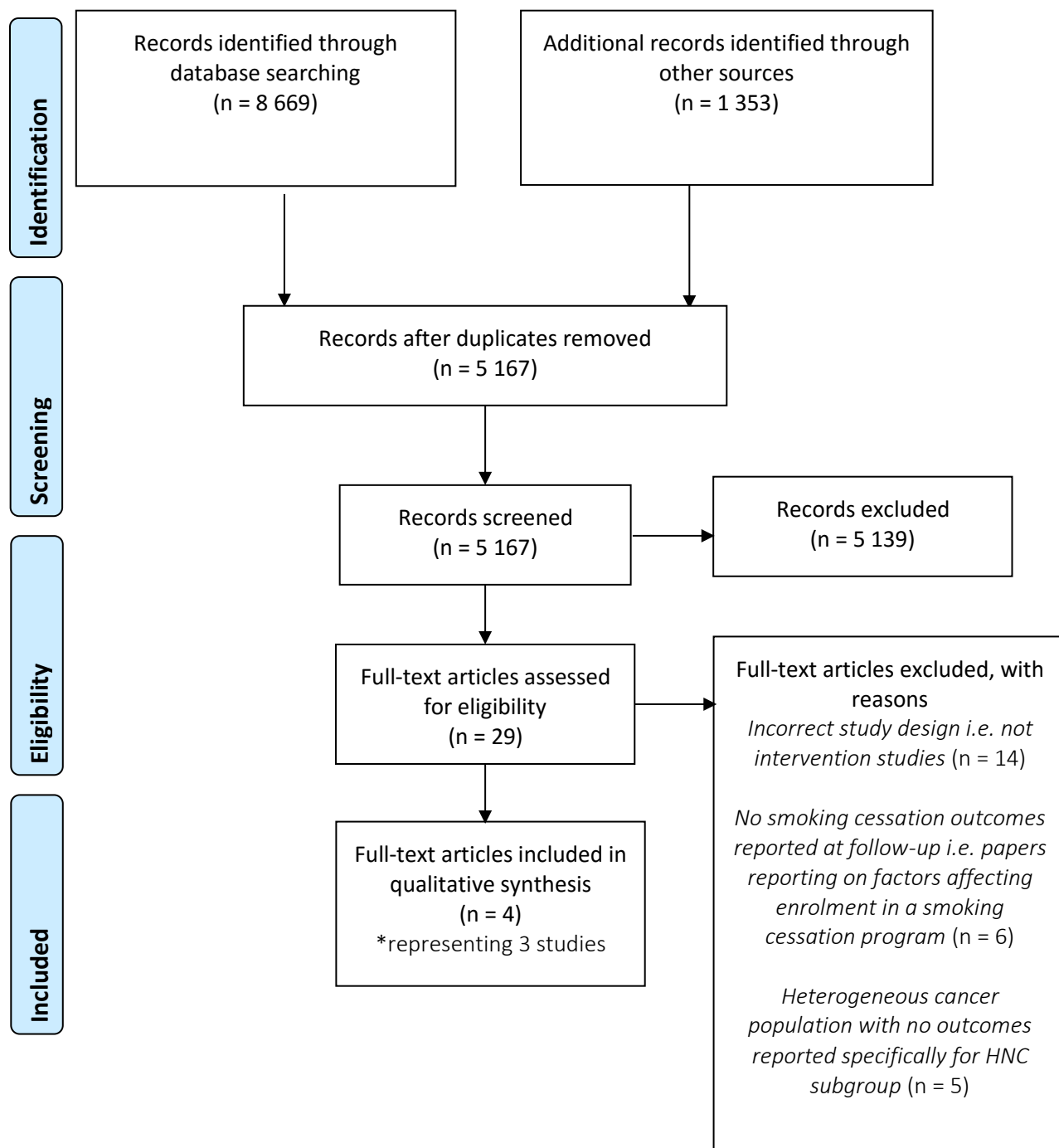
Figure. 1. PRISMA flow chart illustrating study inclusions through the stages of the systematic review.

quantitative studies (30) (Appendix A8, A9). This tool covers any quantitative study design, includes components of intervention integrity and was judged to be suitable to use in systematic reviews of effectiveness (29, 31). Two review authors (KM and UM) independently assessed study quality and discrepancies were resolved through discussion. The EPHPP assesses six methodological dimensions: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. These domains are rated on a three-point scale (strong, moderate, weak) according to pre-defined criteria and procedures recommended for tool use, and then given an overall global rating. Those with no weak ratings were given an overall rating of strong, those with one weak rating were given an overall rating of moderate and those with two or more weak ratings across the six domains were given an overall weak rating. Two additional methodological dimensions provided by the tool are intervention integrity and analyses and these were also completed by the reviewers.

Data analysis

Summary measures

We reported all statistically significant and non-significant outcomes. Due to the clinical and methodological heterogeneity and the small number of studies included in the review, meta-analysis was not performed and the study findings were synthesized narratively.

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RESULTS

Search results

Abstracts of 5167 citations were screened and the full text of 29 manuscripts were sought for further assessment against the review inclusion criteria (Figure. 1). Of these, 4 publications describing 3 trials were included in the review (4, 15, 31, 32).

Study characteristics

A description of the trial characteristics of included studies is provided in Table 1. Included studies were published between 1991 and 2006. Two RCTs (4,, 31) and one non-RCT (15, 32) were identified. All trials compared interventions with a usual care no intervention control. All three studies were conducted in the US. The interventions employed in Gosselin et al. (31) and Gritz et al. (15, 32) targeted smoking cessation alone, whereas the study by Duffy et al. (4) targeted multiple risk behaviours of smoking, alcohol use and depression.

The follow-up periods varied from 1 to 12 months post intervention. All studies were multicentre and participants were recruited from clinics that provided care to HNC patients. Interventions were delivered at the diagnosis/treatment stage of the cancer care continuum, including pre-treatment to posttreatment. Two of the three studies reported the location of the HNC in participants (4, 15). Only one study (15) reported the type of cancer treatment patients received (radiation or surgery). Smoking cessation interventions were delivered by healthcare providers and were either non-pharmacological alone (CBT, self-help material, telephone counselling) or combined with a pharmacological component (NRT, varenicline or

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Table 1. Trial Characteristics

Author year (Ref)	Study type	Study dates	Single-center or multicentre	Setting	Country	Aim	Inclusion criteria	No. of patients at start of intervention n	Mean age (yrs)	Gender M (%)	Tumour site/Tumour stage	Cancer treatment type/Stage of treatment
Duffy et al. 2006 (4)	RCT	2000-2003	Multi (4 hospitals)	ENT clinic, telephone. Four hospitals including the University of Michigan Medical Center and three Veterans Affairs (VA) hospitals in (Ann Arbor, MI, Gainesville, FL, and Dallas, TX)	USA	To develop and test a tailored intervention for patients with HNC that included CBT, nicotine replacement therapy, and selective serotonin reuptake inhibitor management for smoking, alcohol use and depression	Patients with HNC from the time of diagnosis and thereafter who: (a) screened positive for one or more of the three health problems of smoking, alcohol, and depression; (b) were not pregnant; and, (c) were >18 years of age	184 (91 UC; 93 I)	57 years (9.9 SD)	84	Larynx 33%, Oropharynx/ hypopharyn x 30%, Oral cavity/other 37% Stage 0, I or II 39%, stage III, IV 61%	NR/Both new and posttreatment
Gosseli n et al. 2011 (31)	Quasi-experim ental design	patients recruited between: May 2007- June 2007;	Multi (2 clinics)	Dental/ maxillofacial or head and neck clinic, telephone. Roswell Park Cancer Institute (Buffalo, NY)	USA	To evaluate the effectiveness of a brief staff training program on improving the delivery of tobacco cessation services to patients with head and neck cancers	Current tobacco users (i.e., cigarettes, cigar, pipe, smokeless/chew ing tobacco, or some other type of tobacco)	179 (98 UC; 81 EC)	55.8% in 53-60 yrs quartile	86.8	NR/NR	NR/New and established patients

Usual care (UC) group patients Enhance d cessatio n (EC) group

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Study	Design		Setting	Clinic	Country	Aim	Population / Inclusion criteria	Sample	Mean age		Tumour / treatment characteristics
Gritz et al. 1993 (15, 32)	RCT	NR	Multi (10 clinics)	Clinic. Sites included 3 university hospitals (including both the head and neck and the maxillofacial clinics at UCLA, the main site), 3 Veterans Administration medical centers, 2 county hospitals, a health maintenance organization hospital, and an armed services hospital (CA)	USA	Assess the efficacy of a provider-delivered smoking cessation intervention for head and neck cancer patients	Adult (over 18 years of age) patients with newly diagnosed squamous cell carcinomas of the head and neck who met the following criteria: (a) life expectancy of more than 1 year; (b) tobacco use within the past year; (c) absence of gross psychopathology; (d) medical follow-up by local providers; (e) English speaking and reading; and (f) agreement to undergo treatment. A total of 389 eligibility checklists were	186 (92 UC; 94 I)	58.5 years	73.7	Oral Tumors only 28.5% (n = 53), total Laryngectomies 24.7% (n = 46), other than total laryngectomy which may have been followed by radiation Stages I and II 31.1% (n = 57), Stage III 44.3% (n = 81) and Stage IV 24.6% (n = 45) Radiation only 28.5% (n = 53), total cavity 60.9% (Buccal cavity 54.9%, n = 101 and pharynx 6.0%; n = 11) and Laryngeal 39.1% (n = 72) / spanned pretreatment to posttreatment

patients recruited between: July 2007- August 2007

NR, not reported

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Table 2. Intervention description

	Intervention		Description	
	Non-pharmacological	Pharmacological		Control
Duffy et al. 2006 (4)	Nurse administered. CBT workbook, CBT telephone counselling (9-11 sessions).	Those who smoked were offered nicotine replacement therapy and/or bupropion, and those with depression were offered antidepressants.		Enhanced usual care; referred as needed for smoking cessation, and/or alcohol treatment, and/or psychiatric evaluation. Handout for local, state, and national resources tailored to each study site.
Gosselin et al. 2011 (31)	Nurse and physician administered. Inquired about tobacco use, advised patients to quit, and offered assistance to tobacco users interested in quitting. Information packets were made available for staff to give to patients who reported current tobacco use. Attempts to contact all patients by phone within 10 days of visiting the clinic were assigned to a designated researcher who was trained in the delivery of support and cessation counselling components at the New York State Smokers Quitline. They were also contacted 1 month after clinic visit.	Prescription of stop smoking medication for eligible patients; varenicline and bupropion.		Usual care; standard tobacco cessation practices administered by health providers with regard to asking patients about their tobacco use status or providing assistance to quit smoking at Roswell Park Cancer Institute.
Gritz et al. 1993 (15, 32)	Delivered by head and neck surgeons or maxillofacial prosthodontists. Enhanced initial advice (supplemented the usual care advice with a discussion of the subject's receptivity to quitting; a statement of confidence in the subject's ability to stop; presentation of three self-help booklets; a discussion of tobacco withdrawal; a discussion to determine a target quit date, including joint signature of the quit-smoking contract; and an affirmation of continuing provider support during follow-up care) session augmented by six booster sessions.			Usual care; standardized advice consisting of information on the risks of continued smoking and the benefits of cessation for head and neck cancer patients. No guidelines regarding additional advice sessions; providers were free to follow their usual practice regarding discussing patient smoking practices.

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Table 3. Ratings of methodological quality: strong (S), moderate (M) and weak (W).

		Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals	Global rating
1	Duffy et al. (2006) (4)	Weak	Strong	Strong	Moderate	Weak	Strong	Weak
2	Gosselin et al. (2011) (31)	Moderate	Strong	Weak	Moderate	Weak	Moderate	Weak
3	Gritz et al. (1993) (15, 32)	Moderate	Strong	Strong	Weak	Strong	Moderate	Moderate

bupropion) (Table 2). In all studies, the control group received usual care, ranging from information on the risks of continued smoking and the benefits of cessation, to handouts for resources, to referral for smoking cessation treatment.

Methodological quality assessment

Individual ratings for each study against the six methodological criteria and the assigned global rating are reported in Table 3. Overall, two studies received a methodological quality rating of weak (4, 31) and one study received a rating of moderate (15, 32). Unrepresentative samples and non-reporting of blinding of participants and outcome assessors were key issues. Two studies relied solely on self-reported smoking status (4, 31) and one used urinary cotinine to confirm smoking status (15, 32).

The two additional methodological dimensions provided by the EPHPP tool, intervention integrity and analyses were also completed. All three studies measured the percentage of participants that received the intervention as intended and were scored in the 80-100% category on this dimension. With regards to consistency of the interventions, Duffy et al. (4) did not describe whether the intervention was provided to all participants in the same way. Gosselin et al. (31) reported that a proportion of the participants in the intervention condition had multiple clinic visits compared to the other intervention participants who had one visit. Gritz et al. (15, 32) used exit checklists to ensure that their intervention was delivered consistently, with each component delivered to almost all subjects in the intervention condition. However, as the health providers in this study gave advice in both the control and intervention conditions, there was evidence that some contamination may have occurred. Both Duffy et al. (4) and Gosselin et al. (31) used intent to treat analyses as appropriate.

Effects of intervention

Tables 3 and 4 describe the intervention characteristics and results of the included studies respectively. All three included studies reported smoking cessation outcomes. Duffy et al. (4) conducted a RCT to test a tailored smoking, alcohol and depression intervention in 184 HNC patients recruited from four hospitals in the US and conducted in ear, nose and throat clinics. The CBT intervention addressed smoking, alcohol and depression and utilised a workbook for patients and telephone counselling delivered by nurses in combination with NRT and/or bupropion (and antidepressants for depression) to target comorbid conditions (smoking, alcohol use and depression). The control group received enhanced usual care. The primary smoking cessation outcome in this study was self-reported smoking status (patients asked if they were currently smoking) measured at six months post intervention. The authors found that (for the 136 HNC patients that smoked in the past 6 months at baseline) at 6-month follow-up, the intervention group reported significantly higher quit rates than those in the usual care group ((47% vs. 31%, $p<.05$). The authors did not measure any additional outcomes of smoking related behaviour.

Gosselin et al. (31) conducted a study with a quasi-experimental design in 179 HNC patients recruited from a dental/maxillofacial clinic and a head and neck clinic in the US. The study compared the smoking behaviours of those who visited the clinic during a usual care phase (standard tobacco cessation practices) to those who visited the clinic during the intervention phase. The intervention phase employed nurse and physician brief advice to quit, information booklets and pharmacotherapy (varenicline and bupropion) during the clinic visit as well as a follow-up phone call within 10 days after the clinic visit to provide cessation counselling support. The primary smoking cessation

Table 4. Tobacco smoking cessation characteristics

Author year (Ref)	No. of pts at start of intervention	Current smokers at baseline; outcome measure	Usual care (no. of pts) at follow-up	Intervention n (no. of pts) at follow-up	Primary Outcome Description and follow-up interval	Results	Secondary Outcomes Description and follow-up interval	Results
Duffy et al. 2006 (4)	184 (91 I)	148 (68 UC; 80 I); self-report (smoked in the last 6 months)	62/68 (91 including those not 'smokers' at baseline)	74/80 (93 including those not 'smokers' at baseline)	Self-reported smoking status (patients asked if they were currently smoking); 6 months post intervention	Chi-squared tests of association using ITT analysis: significant difference in smoking cessation with 47% (35/74) quit in the intervention group versus 31% (19/62) quit in the usual care group ($p < 0.05$).	Subgroup analyses: Self-reported smoking cessation rates; 6 months post intervention	Smoking cessation rates for only those smokers with comorbid depression and/or alcohol (omitting those who smoked only; n = 101), the quit rates remained higher in the intervention group (48%) compared with the usual care group (26%; $P < 0.05$). All patients who smoked in the last 6 months were included as smokers and, as expected, those who smoked more recently were significantly less likely to quit in both the enhanced usual care and intervention groups ($p < 0.001$).
Gosselin et al. 2011 (31)	179 (98 UC; 81 EC)	179 (98 UC; 81 EC); self-report current tobacco use (105 cigarette, 2 cigar, 1 pipe, 1 chew)	60/98	52/81	Self-reported smoking status (patients asked if they were currently smoking); 1-month post intervention	Chi-square statistic was used to evaluate differences between the EC and UC groups on smoking behavior reported. Non ITT quit rates (assumption that those	Self-reported quit attempt (those who reported that they were currently smoking were subsequently asked whether or not they had made any attempt to stop smoking during the past	Chi-square statistic was used to evaluate differences between the EC and UC groups on smoking behavior reported. Quit attempts at 1-month: I, 56% vs.

Study	Sample	Assessment / definitions	Outcome	Results
Gritz et al. 1993 (15, 32)	186 (94 UC; 92 I)	164, self-report (currently smoking or stopped smoking less than 1 month prior to the baseline interview. | Smoking cessation; | No significant differences between intervention and control at any follow up on any of the three smoking cessation outcomes. | lost to follow-up were missing at random): EC, 14% vs. UC, 13% at 1 mth (NS). ITT quit rates (assumption that those lost to follow-up had all returned to smoking): EC, 9% vs. UC, 8% at 1 mth (NS).	month); 1-month follow-up post intervention	UC, 55% (NS).
		56/92	Ever quit (abstinent for 48 consecutive h or longer at any time during the 12-month follow-up post intervention period after receiving initial smoking cessation advice)	I, 80% vs 79.8% at 1 mth (NS) I, 84.3% vs UC, 82.6% at 6 mth (NS), I, 91.4% vs UC, 89.3% at 12 mth (NS).	Consumption of cigarettes per day	Subjects who were smoking at 12-month follow-up (n = 30) had significantly reduced their consumption during the study, from 25.4 cigarettes/day (SD = 12.8) at baseline to 12.5 (SD = 8.1) at 12 months (t = 7.67; p = 0.0001). No significant difference between I and UC subjects.
		58/94	Point prevalence abstinence (abstinent for 48 h or longer at the time of the follow-up interview); 1-, 6-, or 12-month follow-up interview);	I, 69.4% vs UC, 76.2% at 1 mth (NS) I, 71.4% vs UC, 73.9% at 6 mth (NS), I, 69% vs UC, 78.6% at 12 mth (NS).	Stage of change; 12-month follow-up (for subjects who were current smokers at baseline n = 96)	χ^2 of the discrepancy between larger number of precontemplators in I group and larger number of subjects in the action stage of change in UC group (p = 0.017).
			Continuous abstinence (abstinent at the interview with no smoking at all after cessation); 1-, 6-, and 12-month	I, 69.4% vs UC, 75% at 1 mth (NS). I, 64.3% vs UC, 71% at 6 mth (NS), I, 63.8% vs UC 76.8% at 12 mth (NS).	Predictors of 12 mth continuous abstinence (applied to the 96 baseline smokers who completed the trial)	Stepwise logistic regression; action stage of change (p = 0.0004) entered the model as significant.

Cotinine validation of self-reported abstinence		Urine samples were collected from 83.8% (258 of 308) of subjects who reported abstinence. Cotinine validations rates were 85.6% at 1 mth, 91.3% at 6 mth, 89.6% at 12 mth..

I, intervention; C, control; UC, usual care; EC, enhanced care; NS, not significant

outcome was self-reported smoking status (patients asked if they were currently smoking) at 1-month post intervention. The intervention was not effective in significantly increasing quit rates at 1-month follow-up with intention to treat (assumption that those lost to follow-up had all returned to smoking) quit rates 8% for the control group compared to 9% in the intervention group. Gosselin et al. (31) also measured self-reported quit attempts (those who reported that they were currently smoking were subsequently asked whether or not they had made any attempt to stop smoking during the past month) at 1-month follow-up post intervention. No significant difference was found between intervention and control groups. No other smoking behaviours were reported.

Gritz et al. (15, 32) conducted a RCT to assess the efficacy of a provider delivered smoking cessation intervention compared to usual care advice in 186 HNC patients recruited from 10 hospital or medical center clinics in the US The intervention group received surgeon delivered enhanced advice (see Table 3) to quit smoking augmented by six monthly booster sessions compared to a usual care control group. The authors reported three smoking cessation outcome measures: a) ever quit (abstinent for 48 consecutive hours or longer at any time during the 12-month follow-up post intervention period after receiving initial smoking cessation advice); b) point prevalence abstinence (abstinent for 48 hours or longer at the time of the 1-, 6-, or 12-month follow-up interviews); and c) continuous abstinence (abstinent at the 1-, 6-, and 12-month interviews with no smoking at all after cessation). Cotinine validation of self-reported abstinence was also conducted at each follow-up point. No significant differences were found for any of the smoking cessation outcomes.

Gritz et al. (15, 32) also measured change in consumption of cigarettes per day from baseline at 12-month follow-up. Subjects who were smoking at 12-month follow-up (n = 30) had significantly reduced their consumption during the study, from 25.4 cigarettes/day at baseline to 12.5 at 12 months (p = 0.0001). However, relative to control group such reductions were not significant. The study also reported readiness to stop using tobacco at baseline by questionnaire and classified according to the Stage of Change theory into four stages: precontemplator (not currently thinking about stopping smoking), contemplator (thinking of stopping within 1 year), action (quit within the past) and maintenance (quit for 6-12 months). The authors reported a relationship between cessation behaviours (at 12-month follow-up) and baseline readiness to change in the 96 patients that were classified as baseline smokers in their study ($p = 0.002$). Rates of continuous abstinence at 12-month follow-up were lowest for those in the precontemplation stage and highest for those in the action stage of change at baseline. No other smoking behaviours were reported as outcomes in the trial.

DISCUSSION

The objective of the present review was to examine the effectiveness of smoking cessation interventions to improve cessation rates in HNC patients. Despite including both randomised and non-randomised trials, the review identified only three eligible studies. Of these, only one reported significant improvements in cessation rates at follow-up. These findings highlight the lack of robust smoking cessation intervention research conducted among HNC patients, a group where ceasing tobacco use is particularly important.

All three studies employed interventions delivered by a health provider involved in the care of HNC patients. Health professionals in the oncology setting are well positioned to deliver smoking cessation interventions and indeed numerous best practice guidelines recommend that those involved in the care of cancer patients assess smoking status and offer support to quit (4). Interestingly, however, trials testing (i) nurse and physician brief advice to quit and information booklets combined with pharmacotherapy; and (ii) surgeon delivered enhanced advice to quit smoking augmented by booster sessions were ineffective. Such findings are consistent with previous trials and reviews of physician and nurse-administered interventions for cancer patients that have found relatively brief interventions are ineffective (34-38). Patients with smoking related cancers generally have high levels of nicotine dependence, affecting quitting success (34, 37). More intensive smoking cessation interventions may be required to improve quit rates in this population.

Indeed, the only study in this review to find statistically significant differences between intervention and control groups on the primary cessation outcome was Duffy et al (4). The intervention used in this study was high intensity and multicomponent, with up to 11 telephone counselling sessions that targeted multiple risk behaviours with CBT and pharmacotherapy. This finding suggests that low intensity or single intervention components that are sufficient for other patient groups may not be adequate to achieve cessation among HNC patients characterised by long histories of heavy smoking and high nicotine dependence (38, 39). Smoking cessation research in hospitalised patients has found intensive smoking cessation interventions, combining behavioural interventions with cessation medication maximises the likelihood of a positive long-term cessation outcome (40-42). Further trials of smoking cessation interventions in

HNC patients are needed to test this hypothesis, specifically, randomized comparisons of long term biochemically verified smoking cessation outcomes between patients receiving high intensity, combined behavioural intervention and pharmacotherapy with low intensity single component interventions.

Our finding also fits with the results of previous research that integrated treatment is effective for co-existing problems (16, 43, 44). The health behaviours of HNC patients, particularly smoking and drinking, are highly interrelated. A large proportion of HNC patients that smoke also have a history of regularly consuming alcohol (21). Difficulties with nutrition due to the malignancy and treatment, have been associated with smoking and problem drinking in HNC (45). Given the co-occurrence of these behaviours in addition to the high rate of depression found in this group, addressing the interaction between smoking, drinking and depression in HNC patients may be more beneficial for smoking cessation outcomes than targeted smoking treatment that ignores these other factors. The authors would cautiously suggest that multicomponent and integrated treatment be clinically recommended where available, whilst the evidence base is improved.

An important limitation of the review was the quality of studies included. Two studies received a methodological rating of weak and one received a rating of moderate. Although two of the three studies used a RCT design, the sample sizes were relatively small with the number of participants below 200 for all three studies. Only Gritz et al. (15, 33) confirmed smoking cessation status with biochemical verification. Biochemical verification of smoking status is recommended in studies of smoking cessation in medical populations with smoking related diseases (46). Research suggests that

biochemical verification of current smoking status among cancer patients can be as much as 20% higher than self-report (47, 48). As such the cessation outcomes reported in the included trials may represent an over estimate. Additionally, varying interventions, outcomes and endpoints, and the limited number of studies precluded quantitative synthesis of the trial findings. While the review methods were based on the Cochrane handbook, the search was restricted to English language, peer reviewed publications. In doing so, the review may not have captured all relevant studies in the field.

Conclusions

There are very few studies evaluating the effectiveness of smoking cessation interventions that report results specific to the HNC population. The results of this review indicate that a multicomponent approach may benefit HNC patients who continue to smoke after diagnosis. However, this finding is based on one study and therefore the current state of evidence does not allow for a recommendation of any specific form of smoking cessation treatment in particular for this cancer group. There is much scope for developing the evidence base in this area. Given the significance of tobacco smoking as a key risk factor for HNC and its impact on treatment outcomes and further disease it is imperative that further studies with strong methodological quality and standardized outcome measures are conducted in this population to guide development of smoking cessation programs.

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DISCUSSION

DISCUSSION

The papers presented in this thesis described a related but not chronological program of research. The thesis endeavoured to identify and address important gaps in the evidence base regarding modifiable behavioural and affect risk factors among a subgroup in the cancer population with unique challenges. It also examined a number of aspects of HNC patient care to improve the clinical outcomes of this patient group, including nutritional management, distress screening and referral and smoking cessation. The included papers therefore present independent research questions. Paper One identified comorbidities that have a substantial impact on HNC patient outcomes; distress (particularly depression), alcohol use and tobacco smoking. Papers Two and Three described current attempts to implement distress screening and referral for cancer patients generally as a means of ensuring the provision of psychosocial support. Having identified significant flaws in existing research, Papers Four and Five described the methods and results of a successful practice change intervention to improve care for HNC patients according to clinical practice guidelines that included significant improvement of distress screening by oncology dietitians. Paper Six described a systematic review of the evidence of effective smoking cessation interventions in HNC to identify future opportunities to address this risk factor among this population. The final section of this thesis will summarise the main findings of the work and discuss the implications for future research and practice.

Main findings

Paper one presented the rates and co-occurrence of three risk factors for HNC: tobacco smoking, alcohol use and depression in a sample of HNC patients. The cross-sectional study undertaken presented the prevalence of these risk factors in 307 HNC patients

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undergoing RT across four hospitals in Australia. Approximately one third of the sample were current smokers, one third were drinking at hazardous levels and approximately one fifth had likely depression.

Notably, this was the first Australian study to present the rates of co-occurrence of these conditions in a HNC sample. Approximately one fifth of the sample scored positive for two or more problems; smoking, hazardous alcohol consumption and probable depression. More specifically, cluster analysis revealed that males may be more likely to exhibit comorbid conditions, and that, if comorbid conditions are present, it may be likely that it tends to occur in the presence of another comorbid condition, rather than in isolation. The findings offer a further insight into a group of male HNC patients that may require additional supports due to co-occurring issues.

The value of multidisciplinary team care for head and neck cancer patients has been acknowledged in the recommendations of several best practice guidelines (1-3). Guideline directed approaches using multidisciplinary teams have been found to reduce time to treatment and improve treatment outcomes (4). Global implementation of this approach has the capacity to improve the lives of patients with HNC. Disciplines usually include otolaryngology, plastic surgery, general surgery, dietetics, speech pathology, radiation oncology and medical oncology. The findings from Paper One further demonstrate the need for greater multidisciplinary input. Given the key risk factors for HNC (alcohol and tobacco use) and their co-occurrence with depression, and therefore the impact that biopsychosocial symptoms may play in the care of the HNC patient, the inclusion of other disciplines such as psychology may warrant further attention.

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Outside of the oncology setting, treatments such as CBT and MI have been employed for smoking, problematic alcohol consumption and depression, and evidence suggests that integrated treatment for comorbid problems is effective (5-7). The co-occurrence of reduced alcohol intake and smoking in our participants prior to baseline, demonstrates the potential for concurrent reductions in smoking and alcohol use in the HNC population. For those HNC patients who continue to smoke, drink alcohol at hazardous levels, or experience depressive symptoms during treatment and particularly those with co-occurrence of these issues, a multicomponent, intensive treatment may be beneficial and should be explored (5). Given that some HNC patients display poor health behaviours that are known to be mediated by psychological status, health behaviour interventions in particular should consider psychological status.

Numerous best practice guidelines recommend that those responsible for the care of cancer patients screen and refer for distress (1, 11).These guideline recommendations are based on evidence that distress in cancer patients may lead to non-adherence to treatment, poorer QoL and may negatively impact survival (10,11) as well as increase treatment burden to the oncology team and health system (12). Systematic reviews and meta-analyses have demonstrated screening improves the timely management of distress (10, 13), improves adherence to treatment, reduces burden to the treatment team and can avoid progression to more severe anxiety or depression (11). Therefore, recognising and treating distress in cancer populations is an important health priority.

Papers Two and Three described a systematic review of the evidence of the effectiveness of interventions in improving the provision of distress screening referral in

cancer patients. Only five studies met the inclusion criteria and only one of these reported a significant improvement in referrals for psycho-oncological interview for those patients identified as distressed. Paper Three concluded that a need existed for further research into the effectiveness of practice change interventions in increasing provision of distress screening and referral by staff responsible for cancer care. Previous reviews have examined the effects of common distress screening tools such as the DT (1) on cancer patients' outcomes such as QoL or depression (14-18), or the impact of patient reported outcome measures to improve identification of distressed patients and improve treatment decisions (19, 20). In contrast, very little research has been conducted into how to effectively implement distress screening and referral in health settings. Given that distress is now recognised as the sixth vital sign in cancer (21), the findings of the review presented in Paper Three highlighted a major evidence gap that needs to be addressed.

To address the findings of the sub-optimal identification of distress in cancer patients, and the lack of intervention studies aimed at increasing this provision of care, Paper Four described the protocol of a multi-site stepped wedge RCT. The trial examined the effectiveness of evidence based practice change strategies in increasing the delivery of care related to oncology dietitian HNC nutritional management guidelines (including depression screening and referral). The protocol described a trial to be conducted in four Australian RT departments. Practice change strategies were to be implemented to increase the provision of care of six clinical practice guidelines recommendations regarding the frequency of dietitian contact during and after RT, the use of a validated nutritional assessment tool to assess and monitor nutritional adequacy of patients, and

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the screening and referral of patients at risk of distress for psychosocial support. Chart reviews of patient medical records measured the implementation outcomes.

There is a lack of research examining the effectiveness of interventions in increasing the provision of care according to evidence based guidelines in this population and setting. Thus, the intervention strategies were informed by the body of evidence regarding the effectiveness of practice change strategies in clinical guideline implementation and healthcare settings generally (22-31). The practice change strategies used in the trial were: executive support and endorsement (22-23); staff training (26); academic detailing (26-28); systems and prompts (31); performance audit and feedback (26-28); and provision of tools and resources (22, 23, 29-31).

Paper Five described the outcomes of the practice change strategies employed in the trial. The findings of the trial indicated that the clinical practice change strategies were effective in increasing clinician provision of oncology dietitian care for HNC patients according to evidence based nutritional management guidelines, with significant increases in four of the six outcome measures. The greatest improvement was found for patient screening for depression (OR=349; 95% CI: 69, 1756; p<0.0001). Given the need to identify and treat depression in the HNC population, this finding is of great importance. Compared to previous studies that described interventions to improve distress screening and referral for cancer patients identified in Paper Three, the methodology used in the EAT trial was more rigorous, strengthening the evidence base Overall, the findings presented in Paper Five suggest that the intervention addressed many of the commonly reported barriers to the provision of care consistent with guidelines, such as lack of knowledge (30, 231, advice or support (26-28), clinician

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attitudes (31), clinical uncertainty (30, 31) and systems barriers (26-28). Therefore, the practice change intervention described in Paper Five offers one model to support clinicians to improve best practice care for HNC patients.

With the knowledge of the complex relationship between risk factors, namely, depression, alcohol use and tobacco smoking for the development, recurrence and treatment outcomes of HNC, this thesis aimed to take first steps in addressing this multifaceted challenge for patients, clinicians and researchers alike. Having successfully improved oncology dietitian provision of care according to HNC best practice guidelines, the next phase of this work beginning with Paper Six, targets smoking cessation care, another component of HNC care that despite being internationally recognised as imperative (32-34), is sub-optimally delivered. Only three studies were included in the review described in Paper Six. The one study (8) that reported a significant increase in smoking cessation rates was a RCT of a high intensity, multi-component nurse delivered intervention combining CBT and pharmacotherapy for multiple risk behaviours (smoking, alcohol use and depression). The paper concluded that a need existed for further studies with robust methodology conducted in HNC patients specifically.

Implications for practice and research

The findings of this thesis have a number of implications for clinicians and implementation researchers with regard to a need for (i) identification of specific support strategies that increase or maintain the implementation of best practice care for HNC patients; (ii) comparative effectiveness research; iii) implementation of multiple

guidelines corresponding to comorbidity in HNC; and (iv) sustainability of such implementation interventions.

Identification of specific support strategies that increase or maintain the implementation of best practice care for HNC patients

The United States Institute of Medicine Report identified that despite its recommendation that guidelines developed on the best available evidence for cancer management are used, an evidence practice gap remains in clinicians' adherence to these guidelines (35). The Report further described translation of evidence into clinical practice and performance improvement as integral to improving the quality of cancer care. Paper Five utilised a comprehensive, multi-strategic strategy to improve clinician adherence to best practice guidelines for the nutritional management of HNC patients. While effective, the specific intervention components that yielded improvement in care remains unknown.

It is important to learn how successful interventions achieve their effects in order to advance knowledge, guide future research and to inform clinical applications (36, 37). Importantly, understanding how interventions work can inform the development of implementation strategies yielding greater effects or more cost-effective strategies to improve care through identifying elements of an intervention that are critical, and those that can be enhanced or identifying ineffective components that can be removed (37). In the context of finite health resources, the pursuit of more efficient interventions through better understanding of how interventions exert their effects has considerable to improve health system performance and cancer patient outcomes.

Mediation Analysis

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Mediation analysis is a statistical technique that allows researchers to identify the mechanisms by which interventions have their effects (37). While recommended as part of comprehensive evaluations of all clinical trials (36), mediation analyses of trials that seek to improve the provision of care of implementation of guidelines is uncommon (38, 39). It is recommended that development of strategies to improve health professional practice or patient outcomes are guided by theory and mediation analyses may be particularly useful in identifying whether such interventions operate through the pathways hypothesized by the theory on which it was developed.

Behavioural theories such as the theory of planned behaviour have been used in process evaluations of implementation interventions (40-47) suggesting that the effects of such interventions do indeed operate via these constructs. For example, using a survey designed to assess theory based constructs, a 2017 study of 427 general practitioners and practice nurses from the United Kingdom, identified that habit mediates the relationship between planning and healthcare professional guideline-recommended behaviour (47).

The implementation strategies used in the trial described in Papers Four and Five were selected with consideration of a theoretical framework, the Consolidated Framework for Implementation Research (24), and evidence based strategies to address the reported barriers to implementation of evidence based guideline recommendations. These barriers include lack of information, awareness of guideline recommendations and clinical uncertainty, guideline complexity, limited time and a lack of organisational support and resources (31, 48-50). However, the trial did not include an assessment of whether the intervention strategies impacted on the theoretical determinants. Mediation

analysis may be helpful in determining if the effects observed in the trial from Paper Five were mediated by the Consolidated Framework for Implementation Research constructs. This would make an important contribution to the relatively sparse evidence base in this area and could guide future efforts in the field.

Factorial designs

In a 2×2 factorial design, groups of patients are randomised to either intervention A or B, both interventions, or none. Factorial designs are of particular relevance to implementation research. They allow for multiple practice change strategy comparisons that is more time efficient than traditional separate evaluation in two-arm trials (51, 52). Additionally, factorial designs often require smaller sample sizes and therefore have the potential to reduce cost and time for implementation interventions (51), which is of particular interest when deciding how best to change clinician practice. Factorial designs are also attractive when researchers want to test for interactions or moderators of effects (53). There is limited use of factorial designs in implementation research to improve health professional uptake of best practice guidelines (54, 55) and therefore future research may benefit from adopting such methods.

Comparative Research Designs

Implications arising from this body of work can also be considered in relation to comparative effectiveness designs. The Institute of Medicine defines comparative effectiveness research (CER) as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition, or to improve the delivery of care" (56). CER has conventionally been utilised within medical research to assist patients, clinicians and policy makers make informed decisions in discovering alternative treatment approaches

by comparing to usual or best practice care (56). Such designs have shown great benefit in clinical medicine by accelerating improvements in treatment methods, as research is concentrated on interventions that have potential benefits or improvements superior to those of known effectiveness (57). A call has been made to undertake CER of implementation interventions to achieve adoption of evidence based health care into routine practice (58).

CER in the realm of implementation science aims to identify the relative value (including benefit, harms, and/or costs) of alternative efficacious implementation support strategies, generally through direct comparisons (59). CER identifies mechanisms of effect by isolating the effects of various implementation strategies (60). Paper Five described the only known effective HNC implementation intervention for improving care according to dietetic guidelines. Therefore, further research in this area could use a head-to-head comparison of this strategy with an alternative intervention to see if it provides additional benefits above that demonstrated by the approach employed in Paper Five.

Implementation of multiple guidelines corresponding to comorbidity in HNC
Recommendations of a report by the Institute of Medicine recognise that we need to embrace the complexities and challenges of studying and managing comorbidity in cancer (35). Cancer patients with comorbidity are less likely to receive curative treatment for their cancer than those without and comorbidity has consistently been found to have an adverse impact on cancer survival (61). Given the considerable burden and relatively high mortality rate in HNC, identifying and addressing the prevalence and co-occurrence of modifiable risk factors is a priority.

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Paper One provided some of the first evidence for the co-occurrence of smoking, alcohol use and depression in HNC patients in Australia. Providing intervention such as screening, referral for support, brief advice, education and counselling to modify risk factors related to HNC patient health and mood is evidence-based best practice according to numerous guidelines for the management of HNC patients (62-64). Paper Three provided evidence that the delivery of such care for distress is sub-optimal. Paper Five described an effective strategy to improve distress screening and referral in HNC patients. However, provision of care for smoking and alcohol use in oncology settings is also poorly implemented (65-70). There are a number of reasons for this evidence practice gap including health professional lack of time and knowledge about appropriate referral sources (1, 71, 72). Patient-related barriers include stigma, lack of knowledge of treatment options and distance barriers in rural settings (1, 73).

Given the presence of comorbidities in HNC, to provide best practice care, clinicians need to deliver integrated care consisting of multiple best practice guideline recommendations simultaneously. This presents a challenge to the field of implementation research. Diffusion of innovations theory (74), for example, suggests that the greater the complexity of the tasks and demands, the less likely an implementation intervention is to be successful. Implementation trials addressing routine care for behavioural risk factors usually focus on single rather than multiple risks (75-78) and do not focus across the spectrum of care (assessment, brief advice, and referral/follow-up) (75-77). Trials of implementation interventions addressing multiple guidelines, while challenging, may afford the greatest improvements in care provision and deliver the greatest health benefits for patients. Few such trials have been conducted

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(79). McElwaine et al. (80) conducted a two-group (intervention versus control), non-randomised controlled study assessing the effectiveness of a practice change intervention in increasing primary care nursing and allied health clinician provision of preventive care for four health risks. Analyses indicated significant improvements in assessment and brief advice for all risks combined, however the intervention was not effective in increasing referral/follow-up for any of the four risks. The authors concluded that although a implementation strategy was consistent with previous multi strategic approaches that have proved successful in implementation trials addressing single risk factors, when mutiple practice changes are required simultaneously, such support may be insufficient.

Similarly, Bartlem et al. (81) conducted a multiple baseline trial that aimed to determine the effectiveness of an intervention in increasing the provision of preventive care by community mental health clinicians addressing four chronic disease risk behaviours. The intervention included practice change strategies previously found to be effective in health care settings. Following the intervention, there was an increase in assessment for all risks combined, however no significant change in assessment, advice or referral for each individual risk. Importantly, overall, not all intervention strategies were delivered as planned and this inadequate fidelity may, at least in part, explain these findings.

Given the equivocal findings of past implementation strategies on this issue, innovative strategies are required that minimise barriers to multiple guideline adoption. Health information technology approaches may be one such strategy (82-84). In a systematic review of evidence on the effect of health information technology on quality, efficiency, and costs of health care, a major benefit of implementing health information technology

on increased adherence to guideline-based care was demonstrated (85). Decision support, usually in the form of computerised reminders, was a major component of the studies included in the review. The decision support functions were usually embedded in electronic health records in the outpatient setting.

A 2010 Presidential Commission Report in the US on the potential of health information technology emphasised that information technology-enabled health care can reduce fragmentation of information, ensure high-quality and safer care so that clinicians and researchers have access to the informationt they need (86). In order to ensure HNC patients receive appropriate case, coordination of multiple specialities is required. In recognising this challenge, Nouraei et al. (87) implemented a centrally accessible database to reduce delays and provide information expediently to a multidisciplinary team of health professionals. The development of the database intervention was undertaken with careful attention to process workflow planning, coordination among providers, and information accessibility. The database significantly improved cross-speciality coordination, leading to a highly significant reduction in the number of patients whose treatment planning was delayed ($p < 0.001$). The potential benefits of health information technology make it particularly desirable to address the inherent complexities for clinicians addressing multiple comorbidites in the HNC population, including tobacco smoking, alcohol use and depression. Future implementation studies targeting health provider provision of care according to multiple guidelines in HNC may benefit from inclusion of health information technology strategies.

Sustainability of such implementation interventions

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Whilst the clinical practice change strategies employed in Paper Five were effective in significantly improving the odds of implementation of four of the six guideline recommendations targeted, there was a relatively short duration between implementation and follow-up evaluation on guideline use. The introduction of complex workplace change, especially implementing evidence based practice, takes considerable time (88) and we did not measure sustainability of the intervention beyond the study period. To increase uptake of research into practice implementation, interventions aimed at the clinician, organisation, or health system level are often focused on surmounting barriers to their initial implementation (89). However, less research has been conducted to examine the long-term sustainability of implementation interventions (90-93). Sustainability of an implementation intervention can be defined as the extent to which an intervention continues after it has been adopted (74). In order to ensure enduring care provision and consequently long-term quality of care for patients, the sustainability of an implementation intervention is of the utmost importance (94).

Sustainability of interventions is particularly critical in the management of patients with chronic diseases such as cancer. Most research focuses on short-term implementation, yet this does not reflect the needs of the healthcare system or the course of chronic diseases (95). Studies investigating the sustainability of interventions have found that intervention adaptation, fit with context, continual financial support, training, fidelity, and leadership contribute to sustainability (96-98). Campbell et al. (99) conducted an exploratory study to identify critical factors or issues impacting sustainability of the use of the Ottawa Model of Smoking Cessation (OMSC) in hospitals. Hospitals achieved OMSC activity rates that were higher than baseline if they utilised a smoking cessation coordinator with time dedicated to educate and train staff, promoted the OMSC (either

themselves or by enlisting champions), and ensured that patients were being identified, offered counselling, and follow-up. Specific to the clinical practice change intervention employed in Paper Five, additional strategies may also be warranted in future implementations. For example, to ensure sustained improvement in guideline implementation, training "ambassadors" that can then train new dietitians in the guideline recommendations targeted in the EAT trial may represent an effective approach (100, 101). These actions may influence the sustainability of such programs by enhancing the communication between the HNC health risks, stakeholders, and the intervention program.

A number of frameworks for implementing sustainability interventions and for measuring sustainability have been proposed (91, 92, 102, 103). Chambers et al. (91) developed the *Dynamic Sustainability Framework* for sustainability that includes continued learning and problem solving and ongoing modification of interventions. The framework emphasises the fit between interventions and multi-level contexts. The application of such frameworks to the design of future HNC implementation trials provides the potential to significantly improve their effectiveness long-term.

Conclusions

It has been argued that the major socioeconomic, functional and psychological upheaval faced by people with HNC is more traumatic than that for any other form of cancer (104). However, despite the complex, ongoing problems experienced by HNC patients, compared with cancers such as breast and prostate cancer, HNC patients have not had ready access to tailored interventions. This body of work provides information on a unique group with enormous challenges to overcome treatment related side effects as

well as significant comorbidities. Our findings make it even more apparent that much is yet to be done in the area of HNC patient care. Papers One to Five contribute important findings to the evidence base and take steps toward understanding and addressing the complex relationship between health risks and the etiology, recurrence and treatment of HNC. Specifically, this thesis elucidates the prevalence of depression, smoking and alcohol use in this population and takes significant steps toward improving evidence based care for the nutritional and psychosocial management of HNC patients. The recruitment of a large sample of HNC patients, that are often labelled as 'difficult' in clinical research (105), is a major contribution of this thesis to new knowledge. The complex relationships between health and emotional/affect risk factors for HNC are not likely to be addressed simply and quickly and may not be effectively addressed independently.

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APPENDIX A1: Ethics approval for Eating As Treatment trial

9 May 2012

Professor A Baker
Priority Research Centre for Translational Neuroscience & Mental Health
University of Newcastle

Dear Dr Baker,

Re: Eating as treatment (EAT): a stepped wedge, randomised control trial of a health behaviour change intervention provided by dietitians to improve nutrition in head & neck cancer patient undergoing radiotherapy (12/04/18/4.06)

HNEHREC Reference No: 12/04/18/4.06
NSW HREC Reference No: HREC/12/HNE/108

Thank you for submitting the above protocol for single ethical review. This project was first considered by the Hunter New England Human Research Ethics Committee at its meeting held on **18 April 2012.** This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review. The Committee's Terms of Reference are available from the Hunter New England Local Health District website: http://www.hnehealth.nsw.gov.au/Human_Research_Ethics.

I am pleased to advise that following acceptance under delegated authority of the requested clarifications and revised Information Statement by Dr Nicole Gerrand Manager, Research Ethics & Governance, the Hunter New England Human Research Ethics Committee has granted ethical approval of the above project.

The following documentation has been reviewed and approved by the Hunter New England Human Research Ethics Committee:

- For the Participant Information Statement and Consent Form (Version 2 dated 30 April 2012);
- For the Motivational Interviewing Treatment Integrity 3.0 (MITI 3.0) Scale dated 25 June 2007;
- For the following questionnaires:
    - Patient Generated Subjective Global Assessment (PG-SGA);
    - Patient Health Questionnaire 9 (PHQ-9);
    - Agnew Relationship Measure (Five Item: ARM-5);
    - Fagerstrom test for nicotine dependence;
    - Alcohol Use Disorders Identification Test (AUDIT);

- Common Terminology Criteria for Adverse Events (CTCAE) – Dysphagia;
- Common Terminology Criteria for Adverse Events (CTCAE) – Oral Mucositis;
- Australian Standard of Food Texture;
- Patient Health Questionnaire 2 (PHQ-2)

For the protocol: **Eating as treatment (EAT): a stepped wedge, randomised control trial of a health behaviour change intervention provided by dietitians to improve nutrition in head & neck cancer patient undergoing radiotherapy**

Approval has been granted for this study to take place at the following site:

- **Calvary Mater Newcastle**
- **Hunter New England Mental Health**

Approval from the Hunter New England Human Research Ethics Committee for the above protocol is given for a maximum of **3** years from the date of this letter, after which a renewal application will be required if the protocol has not been completed.

The *National Statement on Ethical Conduct in Human Research (2007),* which the Committee is obliged to adhere to, include the requirement that the committee monitors the research protocols it has approved. In order for the Committee to fulfil this function, it requires:

- A report of the progress of the above protocol be submitted at 12 monthly intervals. Your review date is **May 2013.** A proforma for the annual report will be sent two weeks prior to the due date.

- A final report must be submitted at the completion of the above protocol, that is, after data analysis has been completed and a final report compiled. A proforma for the final report will be sent two weeks prior to the due date.

- All variations or amendments to this protocol, including amendments to the Information Sheet and Consent Form, must be forwarded to and approved by the Hunter New England Human Research Ethics Committee prior to their implementation.

- The Principal Investigator will immediately report anything which might warrant review of ethical approval of the project in the specified format, including:

  - any serious or unexpected adverse events

    - Adverse events, however minor, must be recorded as observed by the Investigator or as volunteered by a participant in this protocol. Full details will be documented, whether or not the Investigator or his deputies considers the event to be related to the trial substance or procedure. These do not need to be reported to the Hunter New England Human Research Ethics Committee

    - Serious adverse events that occur during the study or within six months of completion of the trial at your site should be reported to the Manager, Research Ethics & Governance, of the Hunter New England Human Research Ethics Committee as soon as possible and at the latest within 72 hours.

    - All other safety reporting should be in accordance with the NHMRC's Safety Monitoring Position Statement – May 2009 available at

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- Serious adverse events are defined as:

    - Causing death, life threatening or serious disability.
    - Cause or prolong hospitalisation.
    - Overdoses, cancers, congenital abnormalities whether judged to be caused by the investigational agent or new procedure or not.

  - Unforeseen events that might affect continued ethical acceptability of the project.

- If for some reason the above protocol does not commence (for example it does not receive funding); is suspended or discontinued, please inform Dr Nicole Gerrand, as soon as possible.

You are reminded that this letter constitutes ethical approval only. You must not commence this research project at a site until separate authorisation from the Chief Executive or delegate of that site has been obtained.

A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

Should you have any concerns or questions about your research, please contact Dr Gerrand as per the details at the bottom of the page. The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Please quote **12/04/18/4.06** in all correspondence.

The Hunter New England Human Research Ethics Committee wishes you every success in your research.

Yours faithfully

For: Associate Professor M Parsons
         Chair
         Hunter New England Human Research Ethics Committee

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HUMAN RESEARCH ETHICS COMMITTEE

THE UNIVERSITY OF
NEWCASTLE
AUSTRALIA

Notification of Expedited Approval

To Chief Investigator or Project Supervisor:	**Professor Amanda Baker**
Cc Co-investigators / Research Students:	**Associate Professor Judith Bauer** **Doctor Luke Wolfenden** **Doctor Chris Wratten** **Mr Ben Britton** **Doctor Patrick McElduff** **Doctor Ali Beck** **Conjoint Professor Gregory Carter**
Re Protocol:	**Eating As Treatment (EAT): A stepped wedge, randomised control trial of a health behaviour change intervention provided by dietitians to improve nutrition in head and neck cancer patients undergoing radiotherapy**
Date:	**22-May-2012**
HREC Reference No:	**H-2012-0150**
External HREC Reference No:	**12/04/18/4.06**
Date of Initial Approval:	**22-May-2012**

Thank you for your **Initial Application** submission to the Human Research Ethics Committee (HREC) seeking approval in relation to the above protocol.

Your submission was considered under **Expedited Review of External Approval** review by the Chair/Deputy Chair.

I am pleased to advise that the decision on your submission is **External HREC Approval Noted** effective **22-May-2012**.

In approving this protocol, the Human Research Ethics Committee (HREC) is of the opinion that the project complies with the provisions contained in the *National Statement on Ethical Conduct in Human Research, 2007*, and the requirements within this University relating to human research.

As the approval of an External HREC has been "noted" the approval period is as determined by that HREC.

The full Committee will be asked to note this decision at its next scheduled meeting. A formal *Certificate of Approval* will be available upon request. Your approval number is **H-2012-0150**.

PLEASE NOTE:
As the HREC has "noted" the approval of an External HREC, progress reports and reports of adverse events are to be submitted to the External HREC only. In the case of Variations to the approved protocol, or a Renewal of approval, you will apply to the External HREC for approval in the first instance and then Register that approval with the University's HREC.

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Linkage of ethics approval to a new Grant

HREC approvals cannot be assigned to a new grant or award (ie those that were not identified on the application for ethics approval) without confirmation of the approval from the Human Research Ethics Officer on behalf of the HREC.

Best wishes for a successful project.

Professor Allyson Holbrook
Chair, Human Research Ethics Committee

For communications and enquiries:
Human Research Ethics Administration

Research Services
Research Integrity Unit
HA148, Hunter Building
The University of Newcastle
Callaghan NSW 2308
T +61 2 492 18999
F +61 2 492 17164
Human-Ethics@newcastle.edu.au

Linked University of Newcastle administered funding:

Funding body	Funding project title	First named investigator	Grant Ref
National Health & Medical Research Council/Project Grant(**)	Eating As Treatment (EAT): A stepped wedge, randomised control trial of a health behaviour change intervention provided by dietitians to improve nutrition in head and neck cancer patients undergoing radiotherapy	Baker Amanda,	G1100093

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APPENDIX A2: Information and consent form for Eating As Treatment trial

PARTICIPANT INFORMATION SHEET

EAT

Coordinated by the Priority Research Centre for Translational Neuroscience and Mental Health (CTNMH), University of Newcastle in collaboration with Hunter New England Health, The University of Queensland and the Trans-Tasman Radiation Oncology Group (TROG).

1. Invitation

You are invited to take part in a research trial, also known as a clinical trial or 'study'. Before you decide if you would like to take part in the study you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully and to decide if you wish to take part in the study. Talk to others about the study if you wish and feel free to ask us if there is anything that is not clear or if you would like more information. You can use family support or a friend to help ask questions and understand the study. Your participation in this study is voluntary and you can withdraw at any time. A total of 400 patients will participate in this study.

2. Why have I been invited?

You have been invited to participate in this study because you have been diagnosed with head and neck cancer and have been scheduled to undergo radiotherapy.

3. What is the purpose of this research study?

The purpose of this study is to investigate whether a dietitian delivered 'health behavior intervention' will help to improve nutrition amongst patients with head and neck cancer. Malnutrition is a major problem for people with head and neck cancer. The cancer itself can cause difficulty eating, fatigue, loss of appetite and weight loss. Similar nutritional problems are also a side effect of treatment. When patients experience malnutrition, their immune function is also compromised. This means that they are more likely to experience complications during treatment and their treatment may not be as effective. Evidence suggests that one way to improve nutrition amongst head and neck cancer patients may be to change the way that nutrition interventions are delivered. In the current study we will

work with dietitians to modify the way they currently deliver their sessions to see if this helps to improve the nutritional status of their patients.

4. What does this study involve?

This study is a 'stepped wedge randomized trial' - All participating hospitals will start in the 'treatment as usual' condition. That is, dietetic consultations will be consistent with standard practice for that hospital. At a random point in time, the dietitians will receive training from the research team and begin to implement the 'EAT' intervention. We will collect information from patients before and after the dietitians have received the training. This will allow us to compare current practice with the EAT intervention to see if there is any additional benefit from adding EAT to usual care.

The main difference between 'treatment as usual' and 'EAT' is the way that dietitians deliver their sessions. EAT is designed to be used during standard dietetic practice. Irrespective of whether your dietitian has received training, you can be assured that you will receive the standard level of care provided at your hospital.

You will not know whether you are receiving standard treatment or whether your dietitian has received the training. Knowing whether your dietitian has received training might change your relationship with them, or it could alter your treatment expectations. Not telling patients whether their dietitian was trained in the EAT intervention means that we can more clearly measure whether the training has been helpful.

If you decide to take part in the study:

> Participants will be involved in the study for approximately 18 weeks - during radiotherapy treatment and then follow-up appointments with a research officer after the completion of radiotherapy at four week, six week and three month intervals.

> Consent: You will be asked by a research officer to read this information statement and sign the consent form. Please make sure that any questions you might have are answered to your satisfaction before you sign the consent form.

> Dietitian Appointments: As part of your usual treatment you will be asked to attend up to 13 appointments with a dietitian. The dietitian will monitor your nutrition and talk to you about your nutritional needs. The dietitian will also administer a brief two item questionnaire to screen for symptoms of depression. If your responses to this questionnaire suggest that you may benefit from additional support, the dietitian will contact your radiation oncologist. Your dietitian and/ or radiation oncologist may then discuss additional support options with you.

APPENDIX A2: Information and consent form   A   7

Audio-taping dietitian appointments: We would like to ask for your permission to audiotape the dietetic appointments you are involved in as part of this study. The purpose of audio-taping the session is for supervision to be provided to your dietitian to ensure that they are providing you with the best possible treatment. The tapes will also be listened to by at least two independent researchers to determine whether the appointment sounds like 'treatment as usual' or the 'EAT' intervention. Audiotapes will be marked with a participant identification number, the initials of the dietitian, and the date and number of the appointment. No personal details about you will be associated with the labeling of these audiotapes. Audiotapes will be securely stored in an electronic data management system and will only be accessible to members of the research team. Any hard-copies will be securely stored in a locked filing cabinet accessible only to the members of the research team. Audio recordings will be kept until the conclusion of the study (approximately June 2015).

Please note that you are under no obligation to consent to the audio-taping of your dietetic appointments. You may participate in the study without having your dietetic appointments audio taped. Please take note of item 8 on the Consent Form attached to this information sheet, which asks you to specifically consent to the audio-taping of your dietetic appointments. You can do this by ticking either "Yes" or "No" at item 8.

If you do agree to have your appointments audio-taped, the dietitian involved in your treatment will give you the opportunity at appointment to revise this decision. You are also free to stop and edit the audiotape at any time during the appointment. In addition, at the conclusion of each appointment, you will be given the opportunity to review the audiotape, and make any deletions you feel are necessary. At this time, you are also able to withdraw your consent for audio-taping, either entirely or just for that particular session.

Oncology Appointments: As part of your usual treatment, you will be asked to attend appointments with a radiation oncologist. A research officer will collect information from your medical records about three of these appointments. People often experience side-effects from radiation therapy. The two side-effects we will collect information on are mucositis (inflammation of the mucous membranes) and dysphagia (difficulty swallowing). The radiation oncologist will assess the presence/ severity of these two side effects. These assessments form part of routine care for patients undergoing radiotherapy.

Research Officer Appointments: In addition to your usual care, you will be asked to attend five appointments with a research officer located at the hospital. These

appointments are expected to take no longer than 20 min to complete. The research officer will ask you to complete up to six brief questionnaires. These questionnaires collect information about depression symptoms, smoking pattern, alcohol use and how you feel you are getting along with the dietitian (the dietitian will not see your responses to this questionnaire). The research officer will also conduct a nutritional assessment, which will involve some questions and a brief, non-invasive physical assessment (e.g. lightly squeezing triceps, ankles and calves) to determine fat, muscle and fluid status. Where possible, the research officer will arrange a convenient time to meet with you on a day when you are already attending an appointment at the hospital. In the event that this is not possible, they will contact you to arrange an alternative time that is convenient for you.

You are welcome to bring your family to all appointments.

6. What are the possible risks from participating in this study?

Changes in mental health symptoms: Sometimes people report that completing self-report measures of depression and modifying their diet is associated with some feelings of discomfort. With your permission, we will keep your oncologist and other relevant health professionals up to date on your progress in the study. We encourage you to maintain contact with these health professionals throughout the study. If you feel your psychological symptoms are increasing, we would also like permission to contact a relevant health care professional to organise emergency assistance, if needed, or other assistance as required.

In addition, although unlikely, there may be risks associated with this study that are presently unknown or unforeseeable.

8. What are the Possible Benefits from participating in this study?

The aim of the study is to further medical knowledge which may improve the treatment of patients with head and neck cancer. It is possible that participating in this study may help you to improve your nutrition. It may also improve the identification of troubling depression symptoms and help to mobilise appropriate treatment. However, we cannot guarantee that you will receive any direct benefits from participating in this study.

9. What are the alternative treatments or procedures (if I don't want to take part in the study)?

No alternative dietetic intervention will be available at hospitals participating in the study. During the 'treatment as usual' phase patients will receive standard care as offered by the hospital. During the 'intervention' phase patients will receive the 'EAT' intervention in addition to the standard care offered by the hospital.

10. What will happen if I don't want to carry on with the study?

Participation in this research is entirely your choice. Only those people who give their informed consent will be included in the study. Whether or not you decide to participate, your decision will not disadvantage you in any way. Withdrawal from the study in any form WILL NOT jeopardise the treatment that you receive now or in the future, your relationship with the staff caring for you, your ongoing care at this hospital, or your relationship with any of the institutions involved in this study.

If you do decide to participate, you may withdraw from the study at any time without giving a reason. You can also request to withdraw all data relating to you. An exception to this is in the case of an adverse event, or a serious adverse event, where the data needs to be retained for regulatory reporting.

The researcher(s) may withdraw a participant if it is considered in the participant's best interest or it is appropriate to do so for other reasons. If this happens, the researcher(s) will explain why and advise you about any follow-up procedures or alternative arrangements as appropriate.

11. How will my confidentiality be protected?

Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. For example, we would legally be required to inform relevant authorities if you indicated that you planned to harm yourself or someone else.

The person interviewing you, the person coordinating the study, and a research team at the University of Newcastle and University of Queensland will have access to your information. The results of the study may be published or discussed, but no individual participating in the study will be identified in any way. That is, only summarised data will be made available from this study.

Hospital staff with access to your medical records may also have access to some information collected as part of this study. To begin with, the research officer will keep the information you provide (e.g. completed questionnaires) in your medical records. This information will be removed at least fortnightly and sent to the trial co-coordinating centre (CTNMH). Before sending this information to the CTNMH, you will be allocated a "participant number". Any identifying details (name, address and contact details) will be removed and your information will be labeled with your participant number. All data at the trial co-coordinating centre will be labeled with your participant number and will be stored separately to your name, address and contact details.

If you join the study, some information in your medical records and the data collected for the study will be looked at by authorised persons as delegated by the CTNMH - the group organising the study. They may also be looked at by representatives of regulatory authorities.

Your doctor may also need to obtain some of your health information from other health service providers such as another hospital, pathology laboratory, radiotherapy centre, your family doctor or a medical specialist.

We would also like to ask you whether we can contact you over the next five years about further research projects. If you agree to be contacted, this does not mean that you have to take part in any future studies. You can decide that at the time. Please take note of item 9 on the Consent Form attached to this information sheet, which asks you to specifically consent to being contacted over the next five years. You can do this by ticking either "Yes" or "No" at item 9.

12. What will happen with the results of the study?
It may be a number of years before the results of this research are available. The information collected will be used in a thesis to be submitted for Dr Britton's PhD. We also intend to publish the results of this research in a scientific journal. However, in any publication, information will be provided in such a way that you cannot be identified. In the consent form you are invited to request a description of the study outcome in lay terms which will be sent to you once the study is complete (please indicate "Yes" or "No" at item 10).

We will also ask your consent to use the de-identified data obtained here for a comparison to measures obtained in future studies conducted by the researchers (e.g. students completing honours or masters research projects). This is completely optional and you can participate in this study without providing this permission. Please take note of item 11 on the Consent Form attached to this information sheet, which asks you to specifically consent to using your data in future projects.

15. Will participation cost me anything, and will I be paid?
Participation in this study will not result in any additional expense for you. You will not be paid for your participation in this study.

16. Further information and contact details
Who do I contact for advice?
Please read this information sheet carefully. Feel free to ask for clarification on any aspect of the study that you do not understand. The research officer will answer any questions

you may have. You may also wish to discuss the study with a relative or friend or your local health worker. Feel free to do this. Do not sign the consent form if you have not received satisfactory answers to your questions and/or you have doubts about participating in this study.

If you want to know more about this study or if you have any problems during this study, you can contact one of following people:

Principle Investigator:	**Co-Investigator**	**Trial Coordinator**
Professor Amanda Baker	Dr Benjamin Britton	Dr Alison Beck
(02) 40335690	(02) 4033 5715	(02) 4033 5718
Amanda.Baker@newcastle.edu.au	Ben.Britton@hnehealth.nsw.gov.au	Alison.Beck@newcastle.edu.a

Who do I contact for advice after hours?

If you have any distressing emotional symptoms and need to speak to someone urgently after hours please contact:

Lifeline: [Insert local service]
13 11 14

Who should I contact if I have concerns about the conduct of the study?

If you have any complaints about any aspect of the study, the way it is being conducted or any questions about your rights as a research participant, then you may contact:

Ethics Coordinator:	**Patient Advocate:**
[Insert Name]	[Insert Name]
[Insert Phone Number]	[Insert Phone Number]
[Insert Email]	[Insert Email]

You will need to tell the Ethics Coordinator or the Patient Advocate the name of the researcher given on page 6 of this Participant Information and Consent Form.

Thank you for taking the time to consider being part of this study.

If you wish to take part in this study, please sign the attached consent form.

This information sheet is for you to keep.

CONSENT FORM

EAT

By signing this consent form:

1. I confirm that I have read, or have had read to me in a language I understand, the Participant Information Sheet (Verson 1, 30 March 2012) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from TROG or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.

4. I give permission for doctors, other health professionals, hospitals or laboratories outside this hospital to release information concerning my disease and treatment that is needed for this study. I understand that such information will remain confidential.

6. I agree to take part in the above study.

7. I understand that I will be given a signed copy of this document to keep.

8. I give permission for my treatment sessions to be audiotaped. I understand that this is only for the purpose of providing supervision and assessing dietitian competence and fidelity to EAT. I understand that audiotapes will not contain any identifying information that links the audiotape to me, and I can ask for the tape to be stopped or sections edited or erased at any time during or after the session.

   ☐ Yes   ☐ No

9. I give my permission to be contacted over a five- year period following completion of this study regarding future research projects. This includes contacting my alternate contact person should the researchers not be able to locate you me at my address provided.

   ☐ Yes   ☐ No

10. I would like a copy of the study's results sent to me when available

    ☐ Yes   ☐ No

11. I consent to allow the researchers to use the data collected here for comparison to similar measures used in future studies.

    ☐   Yes   ☐   No

Signatures

Patients (or Guardians) Name	Signature	Date

Witness Name (where required)	Signature	Date

Declaration by the Interpreter

I hereby declare that I was present and interpreted for the informed consent process with the patient.

Name of Interpreter (where required)	Signature	Date

Declaration by the Investigator

I hereby declare that I have discussed the purpose, procedures and risks of this research study with the patient.

Name of Principal Investigator/Delegate	Signature	Date

REVOCATION OF CONSENT FORM

EAT

By signing this consent form I give notice to;

(Please initial one)

☐   **Withdraw** from research appointments in the study named above.
I do not wish to participate in any further research related follow-up visits with the research officer. I do not wish to have any further information collected for the study. However, I consent to the research team using any data collected thus far.

☐   **Totally withdraw** my consent to participate in the study named above. I do not wish to attend study related follow up assessments and wish to withdraw my data from the study. I understand that such withdrawal WILL NOT jeopardise the treatment that I receive now or in the future, my relationship with the staff caring for me or my ongoing care at this hospital..

_____
Patients (or Guardians) Name   Signature   Date

Declaration by the Interpreter

I hereby declare that I was present and interpreted for the trial participants' withdrawal of consent.

_____
Name of Interpreter (where required)   Signature   Date

APPENDIX A3: Study assessment measures for Eating As Treatment trial

Participant Number: ☐☐☐☐

Date of Assessment: ☐☐ / ☐☐ / ☐☐☐☐

Interviewer's Initials: ☐☐

Location: _____

APPENDIX A3: Study assessment measures

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To be completed by the data manager:

1. Demographic characteristics
2. Nutrition Assessment
   a. PG-SGA
3. Dysphagia
   a. Australian Standard of Food Texture
4. Alcohol dependence
   a. AUDIT
   b. Audit Consumption & Readiness to change
5. Nicotine and CO Measures

To be completed by the participant:
6. Nicotine dependence
   a. FTND
7. Depression
   a. PhQ-9
8. Quality of Life
   a. QLQ-C30
9. Therapeutic Alliance
   a. ARM-5 -
      Note, the ARM-5 must be completed <u>during the first week of radiotherapy</u> <u>*after* the patient has completed their first dietetic appointment</u>

To be completed by the Radiation Oncologist:

10. Dysphagia
    a. CTCAE: Mucositis and dysphagia

To be completed by the Dietitian:

11. Therapeutic Alliance
    a. ARM-5 -
       Note, the ARM-5 must be completed by the dietitian <u>during the patients first</u> <u>week of radiotherapy after the dietitian has completed their first consultation</u> <u>with the patient</u>

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ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY   Version 2.3 14/10/2013
Trial Co-ordinator: Alison Beck   Alison.Beck@newcastle.edu.au   (02) 4033 5039

APPENDIX A3: Study assessment measures   A   18

EAT
Radiotherapy Nutrition Project

WEEK ONE RT
DEMOGRAPHICS
To be completed by the Data manager

1. **Gender**: ❑ Female ❑ Male

2. **Could you please tell me how old you are today?** [write age in years] _____

3. **What is your date of birth?**

   | D | D | / | M | M | / | Y | Y |

4. **In which country were you born?**
   ❑ Australia
   ❑ UK & Ireland
   ❑ Other. Please specify_____

5. **Do you usually speak a language other than English at home [i.e. as your primary language]?**
   ❑ Yes [Endorse 'Yes' *only* if English is *not* the primary language]
   ❑ No

6. **Are you of Aboriginal or Torres Strait Island origin?**
   ❑ Yes
   ❑ No
   ❑ Unsure

7. **What is your current formal marital status?**
   ❑ Married
   ❑ Defacto
   ❑ Widowed
   ❑ Separated but not divorced
   ❑ Divorced
   ❑ Single, never married [If patient responds 'single' clarify with 'have you ever been married' & code accordingly]
   ❑ Other.

8. **What is the level of the highest qualification you have <u>completed</u>?**
   ❑ Primary school
   ❑ Years 7 to 9
   ❑ School Certificate/ Intermediate/ Year 10/ 4th Form
   ❑ HSC/ Leaving/ Year 12/ 6th Form
   ❑ TAFE certificate, diploma, trade certificate or apprenticeship
   ❑ University/ College of Advanced Education/ some other tertiary institute degree or higher
   ❑ Other. Please specify _____

9. **For the past <u>one year</u>, what would be your main type of accommodation?**

   ❑ Private Residence [e.g. Own Home[1], Private Rental][2]
   ❑ Partially Supported Living [e.g. Department of Housing, Independent Unit in Retirement Village/ Nursing Home][2]
   ❑ Fully Supported Living [e.g. Crisis Shelter, Hostel, Hospital, Nursing Home, Residential Treatment Facility]
   ❑ Homeless/ No Fixed Accommodation
   ❑ Other. Please specify _____

   [1] If the patient says they have been living in their own home, clarify whether they own the home or whether they are renting
   [2] If the patient says they are renting, clarify whether this is through a real estate [i.e. private residence] or through department of housing [i.e. partially supported living]

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY
Trial Co-ordinator: Alison Beck
Alison.Beck@newcastle.edu.au

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EAT
Radiotherapy Nutrition Project

WEEK ONE RT
DEMOGRAPHICS
To be completed by the Data manager

---

10. **In the last <u>one year</u>, which of the following options *best describes* your employment status?** [Select one]
    - ❏ No job
    - ❏ Full time
    - ❏ Part time
    - ❏ Housework/ stay at home parent
    - ❏ Studying
    - ❏ Retired
    - ❏ Volunteer
    - ❏ Casual
    - ❏ Other.

11. **In the last <u>one year</u>, what are your main sources of income?** [Select up to three]
    - ❏ Wage/salary from employer
    - ❏ Own business
    - ❏ Pension/ allowance/ benefit →[Specify in Question 13]
    - ❏ Superannuation/ annuity
    - ❏ Workers compensation/ accident or sickness insurance
    - ❏ No income
    - ❏ Other.

12. **Which of the following benefits have you received within the last <u>one year</u>?** [Select up to three]
    - ❏ Age pension
    - ❏ Service pension
    - ❏ Disability support/ invalid
    - ❏ Widows/ wife pension
    - ❏ Carers pension
    - ❏ Sole parent pension
    - ❏ Sickness allowance
    - ❏ Newstart/ job search/ mature age
    - ❏ Unemployment
    - ❏ Other.
    - ❏ NA - No Benefit Received

APPENDIX A3: Study assessment measures   A   20

EAT
Radiotherapy Nutrition Project

WEEK ONE RT
PG-SGA Nutrition Assessment: Patient Generated

1.Weight: In Summary of my current and recent weight:	**2. Food Intake:** As compared to my normal intake, I would rate my food intake <u>during the past month</u> as (tick one response):
I currently weigh about _____ kg	❒ Unchanged
	❒ More than usual
I am about _____ cm tall	❒ Less than usual
or _____ feet ____ inches	
One month ago I weighed about _____ kg	I am now taking (tick one response):
Six months ago I weighed about _____ kg	❒ *normal food* but less than normal amount
During the past two weeks my weight has:	❒ little solid food
(tick one response)	❒ only liquids
❒ Decreased	❒ only nutritional supplements
❒ Not Changed	❒ very little of anything
❒ Increased	❒ only tube feedings or only nutrition by vein
3. Symptoms: I have had the following problems **that have kept me from eating enough during the past two weeks** (Check all that apply)	**4. Activities and Function:** Over the <u>past month</u>, I would generally rate my activity as (tick one response):
❒ No problems eating	❒ Normal with no limitations
❒ No appetite, just did not feel like eating	❒ Not my normal self, but able to be up and about with fairly normal activities
❒ Nausea	
❒ Constipation	❒ Not feeling up to most things, but in bed or a chair less than half the day
❒ Mouth sores	
❒ Things taste funny or have no taste	❒ Able to do little activity and spend most of the day in bed or chair
❒ Problems swallowing	
❒ Vomiting	❒ Pretty much bedridden, rarely out of bed
❒ Diarrhoea	
❒ Dry mouth	
❒ Smells bother me	
❒ Feel full quickly	
❒ Fatigue	
❒ Pain - Specify where:_____	
❒ Other - Specify: *(E.g. depression, money, dental problems)* _____	

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY
Trial Co-ordinator: Alison Beck   Alison.Beck@newcastle.edu.au

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APPENDIX A3: Study assessment measures   A 21

EAT
Radiotherapy Nutrition Project

WEEK ONE RT
PG-SGA Nutrition Assessment
To be completed by the data manager

Worksheet 1- Scoring Weight Loss

To determine the score, use 1 month weight data if available. Use 6 month data only if there is no 1 month weight data. Use the points below to score weight change and add one extra point if patient has lost weight during the past 2 weeks. Enter total point score in Box 1 of the PG-SGA.

Weight loss in 1 month	Points	Weight loss in 6 months
≥ 10%	4	≥ 20%
5-9.9%	3	10-19.9%
3-4.9%	2	6-9.9%
2-2.9%	1	2-5.9%
0-1.9%	0	0-1.9%
	Score for worksheet 1	

Worksheet 2 - Scoring Criteria for Condition

Score is derived by adding 1 point for each of the conditions listed below that pertain to the patient.

Category	Points
Cancer	1
AIDS	1
Pulmonary or cardiac cachexia	1
Presence of decubitus, open wound, or fistula	1
Presence of trauma	1
Age greater than 65 years	1
Score for worksheet 1	

Worksheet 3 - Scoring Metabolic Stress (circle)

Score for metabolic stress is determined by a number of variables known to increase protein & caloric needs. The score is additive so that apatient who has a fever of >102 (3 points) and is on 10mg of prednisone chronically (2 points) would have an additive score for this section of 5 points.

Stress	None (0)	Low (1)	Moderate (2)	High (3)
Fever	no fever	>37 and <38	≥38.5 and <39	≥39
Fever Duration	no fever	<72 hours	72 hours	>72 hours
Corticosteroids	no corticosteroids	low dose (<10mg)	Moderate dose (≥10mg < 30mg)	high dose (≥30mg)
			Score for worksheet 3	

Worksheet 4 - Physical Examination

Physical exam includes a subjective evaluation of 3 aspects of body composition: fat, muscle & fluid status. Since this is subjective, eachaspect of the exam is rated for degree of deficit. Muscle deficit impacts point score more than fat deficit. Definition categories: 0 = no deficit,1+ = mild deficit, 2+ = moderate deficit, 3+ = severe deficit. Rating deficit in these categories is *not* additive but are used to clinically assess the degree of deficit (or presence of excess fluid).

Muscle Status					Fat Stores				
Temples	0	1	2	3	Orbital fat pads	0	1	2	3
Clavicles	0	1	2	3	Triceps skin fold	0	1	2	3
Shoulders	0	1	2	3	Fat overlying lower ribs	0	1	2	3
Interosseous muscles	0	1	2	3	Global fat deficit	0	1	2	3
Scapula	0	1	2	3	Fluid status	0	1	2	3
Thigh	0	1	2	3	Ankle edema	0	1	2	3
Calf	0	1	2	3	Ascites	0	1	2	3
Global Muscle status	0	1	2	3	Global Fluid status rating	0	1	2	3
					Score for worksheet 4				

Work Sheet 5 – Global Assessment (tick one)

☐ A- Well-nourished or anabolic

☐ B- Moderate or suspected malnutrition

☐ C- Severely malnourished

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY
Trial Co-ordinator: Alison Beck   Alison.Beck@newcastle.edu.au

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EAT
Radiotherapy Nutrition Project

WEEK ONE RT
Australian Standardised Terminology & Definitions for Modified Texture Foods and Fluids
To be completed by the Data Manager

UNMODIFIED			MOST MODIFIED
Unmodified Regular Foods	Texture A Soft	Texture B Mince and Moist	Texture C Smooth Pureed

Tick One	Food Texture	Description	Characteristics
☐	**Unmodified Regular foods**	These are everyday foods.	• There are various textures of regular foods. Some are hard and crunchy, others are naturally soft.
☐	**Texture A Soft**	Food in this category may be naturally soft (e.g. ripe banana), or may be cooked or cut to alter its texture.	• Soft foods can be chewed but not necessarily bitten. • Minimal cutting required – easily broken up with a fork. • Food should be moist or served with a sauce or gravy to increase moisture content. (NB: Sauces and gravies should be served at the required thickness level.) • Further instructions in full document. • Targeted particle size for children over 5 years and adults = 1.5x1.5cm (Penman & Thomson, 1998; Samuels & Chadwick, 2006; Kohyama et al., 2002).
☐	**Texture B Minced and Moist**	Food in this category is soft and moist and should easily form into a ball.	• Individual uses tongue rather than teeth to break the small lumps in this texture. • Food is soft and moist and should easily form into a ball. • Food should be easily mashed with a fork. • May be presented as a thick puree with obvious lumps in it. • Lumps are soft and rounded (no hard or sharp lumps). • Further instructions in full document. • Recommended particle size for children over 5 years and adults = 0.5cm (Penman & Thomson, 1998; Mishellany et al., 2006).
☐	**Texture C Smooth Pureed**	Food in this category is smooth and lump free. It is similar to the consistency of commercial pudding. At times, smooth pureed food may have a grainy quality, but should not contain lumps. Refer to Special Note	• Smooth and lump free but may have a grainy quality. • Moist and cohesive enough to hold its shape on a spoon (i.e. when placed side by side on a plate these consistencies would maintain their position without 'bleeding' into one another). • Food could be moulded, layered or piped. • Special Note: Some individuals may benefit from the use of a runny pureed texture. This texture would be prescribed on a case by case basis. (Runny pureed textures do not hold their shape; they bleed into one another when placed side by side on a plate.)
☐	**Nasogastric or PEG Feeding**	Patient unable to tolerate any of the above and is reliant on NGT or PEG feeding	

APPENDIX A3: Study assessment measures   A   23

Site		Participant Number		Completed by (initial/s)	

WEEK ONE RT
Australian Standardised Terminology & Definitions for
Modified Texture Foods and Fluids
To be completed by the Data Manager

Tick One	FluidTexture	Description	Characteristics
☐	**Unmodified Regular fluids**	• There are variable thickness levels in unmodified fluids. Some are thinner (e.g. water, and breast milk) and some are thicker (e.g. fruit nectar). • Unmodified - Regular fluids do not have thickening agents added to them.	• Drink through any type of teat, cup or straw as appropriate for age and skills
☐	**Modified Fluids**	Patient is unable to tolerate water without coughing or choking	•
☐	**Nasogastric or PEG Feeding**	Patient unable to tolerate any of the above and is reliant on NGT or PEG feeding	

APPENDIX A3: Study assessment measures

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Site		Participant Number		Completed by (initial/s)	

WEEK ONE RT AUDIT

To be completed by the Data Manager

Radiotherapy Nutrition Project

This questionnaire contains items designed to assess different patterns of alcohol use. For each question, I would like you to choose the one response that best reflects your typical pattern of alcohol use _over the past year_. Please be as honest as possible and try not to spend too much time thinking about each item. Please let me know if you've got any questions [Data Manager to circle the number next to the relevant statement].

Q1 Over the last year, how often do you have a drink containing alcohol?

0 Never **[Skip to Qs 9-10]**
1 Monthly or less
2 2 to 4 times a month
3 2 to 3 times a week
4 4 or more times a week

Q6 How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?

0 Never
1 Less than monthly
2 Monthly
3 Weekly
4 Daily or almost daily

Q2 Over the last year, how many drinks containing alcohol do you have on a typical day when you are drinking?

0 1 or 2
1 3 or 4
2 5 or 6
3 7, 8, or 9
4 10 or more

Q7 How often during the last year have you had a feeling of guilt or remorse after drinking?

0 Never
1 Less than monthly
2 Monthly
3 Weekly
4 Daily or almost daily

Q3 Over the last year, how often do you have six or more drinks on one occasion?

0 Never
1 Less than monthly
2 Monthly
3 Weekly
4 Daily or almost daily

Q8 How often during the last year have you been unable to remember what happened the night before because you had been drinking?

0 Never
1 Less than monthly
2 Monthly
3 Weekly
4 Daily or almost daily

[Skip to Items 9 & 10 if Total score for Items 2 & 3 = 0]

Q4 How often during the last year have you found that you were not able to stop drinking once you had started?

0 Never
1 Less than monthly
2 Monthly
3 Weekly
4 Daily or almost daily

Q9 Have you or someone else been injured as a result of your drinking?

0 No
2 Yes, but not in the last year
4 Yes, during the last year

Q5 How often during the last year have you failed to do what was normally expected from you because of drinking?

0 Never
1 Less than monthly
2 Monthly
3 Weekly
4 Daily or almost daily

Q10 Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

0 No
2 Yes, but not in the last year
4 Yes, during the last year

APPENDIX A3: Study assessment measures   A 25

Site		Participant Number		Completed by (initial/s)	

WEEK ONE RT
AUDIT-Consumption &
READINESS TO CHANGE

To be completed by the Data Manager

EAT
Radiotherapy Nutrition Project

This questionnaire is also designed to assess different patterns of alcohol use. However, for these questions, I would like you to choose the one response that best reflects your typical pattern of alcohol use *just over the **past two months***. Please be as honest as possible and try not to spend too much time thinking about each item. Please let me know if you've got any questions [Data Manager to circle the number next to the relevant statement].

Q1. **Over the last two months**, how often do you have a drink containing alcohol?

- **0** Never **[Skip to Question B This Page]**
- **1** Monthly or less
- **2** 2 to 4 times a month
- **3** 2 to 3 times a week
- **4** 4 or more times a week

Q2. **Over the last two months**, how many drinks containing alcohol do you have on a typical day when you are drinking?

- **0** 1 or 2
- **1** 3 or 4
- **2** 5 or 6
- **3** 7, 8, or 9
- **4** 10 or more

Q3. **Over the last two months,** how often do you have six or more drinks on one occasion?

- **0** Never
- **1** Less than monthly
- **2** Monthly
- **3** Weekly
- **4** Daily or almost daily

A. **Over the last two months** on a typical day, on average, how many beers, wines and/ or spirits would you have?
[Calculate number of standard drinks]
[To calculate please see Supplementary Resource P22]

	Beer (Number of Standard drinks)	Calculations:
	Wine (Number of Standard drinks)	Calculations:
	Spirits (Number of Standard drinks)	Calculations:

B. Please indicate which of the following statements best reflects your <u>current</u> plan to cut down on drinking (tick one).

- ❑ I am not thinking about cutting down in the near future.
- ❑ I intend to cut down in the next 6 months.
- ❑ I intend to cut down in the next 30 days.
- ❑ I have cut down in the last 6 months.
- ❑ I have cut down for 6 months or more.

APPENDIX A3: Study assessment measures   A   26

Site		Participant Number		Completed by (initial/s)	

WEEK ONE RT
NICOTINE AND CARBON MONOXIDE MEASURES
To be completed by the Data manager

Radiotherapy Nutrition Project — EAT

1. The following test measures carbon monoxide levels related to air quality and smoking. **Carbon monoxide** reading:		PPM		%COHb

2. **Time of day tested?** [enter in 24hr format]   :

3. **Have you been around smokers or in a smoky environment in the last 24 hours?**
   - ❑ Yes
   - ❑ No

4. **Have you ever smoked? [i.e. smoked more than one full cigarette in their lifetime]**
   - ❑ Yes
   - ❑ No

5. **Are you a current smoker?**
   - ❑ Yes
   - ❑ No

6. **How long ago was your most recent cigarette?**   ❑ N/A (non smoker)

   - ❑ < 24 hours → Number of minutes since the most recent cigarette:_____mins
   - ❑ < 2 weeks
   - ❑ < 1 month
   - ❑ < 6 months
   - ❑ < 1 year
   - ❑ < 5 years
   - ❑ > 5 Years

7. **Total number of cigarettes within the last 24 hours [enter the number]** ❑ N/A

8. **Are you currently using nicotine replacement therapy?**   ❑ N/A (non smoker)
   - ❑ Yes
   - ❑ No

If no smoking within the last one month tick 'NA' on FTND and skip to Q7 'Readiness to Change'

APPENDIX A3: Study assessment measures   A   27

Site		Participant Number		Completed by (initial/s)	

WEEK ONE RT
FTND &
READINESS TO CHANGE
To be completed by the participant

EAT
Radiotherapy Nutrition Project

If patient has not smoked a cigarette within the last one month, tick here and skip to Q7 this page

NA

Please read each item carefully and indicate the statement that best applies to you by placing a tick (☑) next to the appropriate statement.

1. **How soon after waking do you smoke your first cigarette?**
   - ☐ Within 5 minutes
   - ☐ 6-30 minutes
   - ☐ 31-60 minutes
   - ☐ 61 minutes or more

2. **Do you find it difficult to abstain from smoking in places where it is forbidden, e.g. church, library etc?**
   - ☐ Yes
   - ☐ No

3. **Which cigarette would you hate to give up?**
   - ☐ The first one in the morning
   - ☐ Any other

4. **How many cigarettes a day do you smoke?** [Please enter the number in the box provided]

5. **Do you smoke more frequently in the morning than in the rest of the day?**
   - ☐ Yes
   - ☐ No

6. **Do you smoke even though you are sick in bed for most of the day?**
   - ☐ Yes
   - ☐ No

---

7. **Readiness to Change**
Please indicate which of the following statements best reflects your current plan to quit smoking (tick).

☐ I am not thinking about quitting in the near future.

☐ I intend to quit in the next 6 months.

☐ I intend to quit in the next 30 days.

☐ I have quit in the last 6 months.

☐ I have quit for 6 months or more.

☐ Not applicable – Never smoked.

APPENDIX A3: Study assessment measures   A   28

Site		Participant Number		Completed by (initial/s)	

WEEK ONE RT
PHQ-9
To be completed by the participant

EAT
Radiotherapy Nutrition Project

Over the last two weeks, how often have you been bothered by any of the following problems? (please circle the number that best applies to you)	Not at all	Several Days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself in some way	0	1	2	3

APPENDIX A3: Study assessment measures   A   29

Site		Participant Number		Completed by (initial/s)	

WEEK ONE RT
EORTC QLQ-C30

To be completed by the participant

Radiotherapy Nutrition Project

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

APPENDIX A3: Study assessment measures   A   30

WEEK ONE RT
EORTC QLQ-C30
To be completed by the participant

EAT
Radiotherapy Nutrition Project

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

<div style="text-align:center">

1   2   3   4   5   6   7

Very Poor   Excellent

</div>

30. How would you rate your overall quality of life during the past week?

<div style="text-align:center">

1   2   3   4   5   6   7

Very Poor   Excellent

</div>

APPENDIX A3: Study assessment measures   A 31

Site		Participant Number		Completed by (initial/s)		Date of Most Recent Appointment	

WEEK ONE
ARM-5: PATIENT

Date:_____

Based on your most recent session with your dietitian, please indicate how strongly you agree or disagree with each statement. Please make sure you respond to *every* statement. Please be assured that your responses to this questionnaire will not be shared with your dietitian.

	Strongly Disagree	Moderately Disagree	Slightly Disagree	Neutral	Slightly Agree	Moderately Agree	Strongly Agree
1. My dietitian is supportive	1	2	3	4	5	6	7
2. My dietitian and I agree about how to work together	1	2	3	4	5	6	7
3. My dietitian and I have difficulty working jointly as a partnership	1	2	3	4	5	6	7
4. I have confidence in my dietitian and his/ her techniques	1	2	3	4	5	6	7
5. My dietitian is confident in him/ herself and his/ her techniques	1	2	3	4	5	6	7

APPENDIX A3: Study assessment measures   A   32

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(REVERSE OF ARM-5)

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY
Trial Co-ordinator: Alison Beck

Alison.Beck@newcastle.edu.au

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APPENDIX A3: Study assessment measures

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WEEK ONE RT
CTCAE: MUCOSITIS & DYSPHAGIA
To be completed by the Radiation Oncologist

		DYSPHAGIA: CIRCLE ONE GRADE				
	0	1	2	3	4	5
DYSPHAGIA	Absent	Symptomatic, able to eat regular diet	Symptomatic and altered eating/swallowing	Severely altered eating/swallowing; tube feeding or TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by difficulty in swallowing.						
		MUCOSITIS: CIRCLE ONE GRADE FOR EACH TYPE				
	0	1	2	3	4	5
MUCOSITIS ORAL	Absent	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death
	0	1	2	3	4	5
LARYNGEAL MUCOSITIS	Absent	Endoscopic findings only; mild discomfort with normal intake	Moderate discomfort; altered oral intake	Severe pain; severely altered eating/swallowing; medical intervention indicated	Life-threatening airway compromise; urgent intervention indicated (e.g., tracheotomy or intubation)	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the larynx.						
	0	1	2	3	4	5
PHARYNGEAL MUCOSITIS	Absent	Endoscopic findings only; minimal symptoms with normal oral intake; mild pain but analgesics not indicated	Moderate pain and analgesics indicated; altered oral intake; limiting instrumental ADL	Severe pain; unable to adequately aliment or hydrate orally; limiting self care ADL	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an inflammation involving the mucous membrane of the pharynx.						

APPENDIX A3: Study assessment measures   A   34

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(REVERSE OF CTCAE)**

APPENDIX A3: Study assessment measures   A   35

Site		Participant Number		Completed by (initial/s)		Date of Most Recent Appointment	

WEEK ONE
ARM-5: DIETITIAN
To be completed by the Dietitian

Date:_____

Based on your most recent session with your patient, please indicate how strongly you agree or disagree with each statement. Please make sure you respond to *every* statement. Please be assured that your responses to this questionnaire will not be shared with your patient

	Strongly Disagree	Moderately Disagree	Slightly Disagree	Neutral	Slightly Agree	Moderately Agree	Strongly Agree
1. I feel supportive	1	2	3	4	5	6	7
2. My patient and I agree about how to work together	1	2	3	4	5	6	7
3. My patient and I have difficulty working jointly as a partnership	1	2	3	4	5	6	7
4. My patient has confidence in me and my techniques	1	2	3	4	5	6	7
5. I feel confident in myself and my techniques	1	2	3	4	5	6	7

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY
Trial Co-ordinator: Alison Beck

Alison.Beck@newcastle.edu.au

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APPENDIX A3: Study assessment measures   A   36

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(REVERSE OF ARM-5)

APPENDIX A3: Study assessment measures   A   37

SUPPLEMENTARY RESOURCE FOR
AUDIT & AUDIT CONSUMPTION

NUMBER OF STANDARD DRINKS – BEER

1.1 285ml Full Strength 4.8% Alc. Vol	**0.8** 285ml Mid Strength 3.5% Alc. Vol	**0.6** 285ml Low Strength 2.7% Alc. Vol
1.6 425ml Full Strength 4.8% Alc. Vol	**1.2** 425ml Mid Strength 3.5% Alc. Vol	**0.9** 425ml Low Strength 2.7% Alc. Vol
1.4 375ml Full Strength 4.8% Alc. Vol	**1** 375ml Mid Strength 3.5% Alc. Vol	**0.8** 375ml Low Strength 2.7% Alc. Vol

1.4 375ml Full Strength 4.8% Alc. Vol	**1** 375ml Mid Strength 3.5% Alc. Vol	**0.8** 375ml Low Strength 2.7% Alc. Vol
34 24 x 375ml Full Strength 4.8% Alc. Vol	**24** 24 x 375ml Mid Strength 3.5% Alc. Vol	**19** 24 x 375ml Low Strength 2.7% Alc. Vol

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

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NUMBER OF STANDARD DRINKS – WINE

1.5
150ml
Average
Restaurant Serving
of Red Wine
13% Alc. Vol

1
100ml
Standard Serve
of Red Wine
13% Alc. Vol

0.8
60ml
Standard Serve
of Port
17.5% Alc. Vol

1.4
150ml
Average
Restaurant Serving
of White Wine
11.5% Alc. Vol

0.9
100ml
Standard Serve
of White Wine
11.5% Alc. Vol

1.4
150ml
Average Restaurant
Serve of Champagne
12% Alc. Vol

7.1
750ml
Bottle of Champagne
12% Alc. Vol

7.7
750ml
Bottle of Red Wine
13% Alc. Vol

41
4 Litres
Cask Red Wine
13% Alc. Vol

21
2 Litres
Cask Red Wine
13% Alc. Vol

6.8
750ml
Bottle of White Wine
11.5% Alc. Vol

36
4 Litres
Cask White Wine
11.5% Alc. Vol

18
2 Litres
Cask White Wine
11.5% Alc. Vol

28
2 Litres
Cask of Port
17.5% Alc. Vol

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY   Version 2.3 14/10/2013
Trial Co-ordinator: Alison Beck   Alison.Beck@newcastle.edu.au   (02) 4033 5039

APPENDIX A3: Study assessment measures   A   39

NUMBER OF STANDARD DRINKS – SPIRITS

These are only an approximate number of standard drinks. Always read the container for the exact number of standard drinks.

* Ready-to-Drink

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY   Version 2.3 14/10/2013
Trial Co-ordinator: Alison Beck   Alison.Beck@newcastle.edu.au   (02) 4033 5039

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(REVERSE OF SUPPLEMENTARY RESOURCE FOR
AUDIT & AUDIT CONSUMPTION]**

ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY   Version 2.3 14/10/2013
Trial Co-ordinator: Alison Beck   Alison.Beck@newcastle.edu.au   (02) 4033 5039

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ASSESSMENT OCCASION: WEEK ONE RADIOTHERAPY
Trial Co-ordinator: Alison Beck

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APPENDIX A3: Study assessment measures   A   42

APPENDIX A4: PROSPERO registration for Paper Two and Paper Three

UNIVERSITY *of York*
Centre for Reviews and Dissemination

NHS
National Institute for
Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1. **Review title**
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Interventions to improve screening and appropriate referral of patients with cancer for distress: systematic review protocol

2. **Original language title**
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. **Anticipated or actual start date**
Give the date when the systematic review commenced, or is expected to commence.
30/04/2015

4. **Anticipated completion date**
Give the date by which the review is expected to be completed.
01/08/2017

5. **Stage of review at time of this submission**
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started   √

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6. **Named contact**
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Miss McCarter

7. **Named contact email**
Enter the electronic mail address of the named contact.
kristen.mccarter@newcastle.edu.au

8. **Named contact address**
Enter the full postal address for the named contact.
CTNMH, Level 5, McCauley Centre, Mater Hospital, C/O: The Store, Platt Street, Mater Hospital, Waratah NSW 2298 Australia

9. **Named contact phone number**
Enter the telephone number for the named contact, including international dialing code.
6140335692

10. **Organisational affiliation of the review**
Full title of the organisational affiliations for this review, and website address if available. This field may be completed

as 'None' if the review is not affiliated to any organisation.
University of Newcastle, Australia

Website address:

11   Review team members and their organisational affiliations
     Give the title, first name and last name of all members of the team working directly on the review. Give the
     organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Miss	Kristen	McCarter	University of Newcastle
Dr	Ben	Britton	University of Newcastle
Professor	Amanda	Baker	University of Newcastle
Dr	Sean	Halpin	University of Newcastle
Dr	Alison	Beck	University of Newcastle
Professor	Gregory	Carter	University of Newcastle
Dr	Chris	Wratten	Calvary Mater Newcastle Hospital
Dr	Judy	Bauer	The University of Queensland
Ms	Debbie	Booth	University of Newcastle
Miss	Erin	Forbes	University of Newcastle
Dr	Luke	Wolfenden	University of Newcastle

12   Funding sources/sponsors
     Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating,
     managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the
     individuals or bodies listed should be included.
     None

13   Conflicts of interest
     List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic
     investigated in the review.
     Are there any actual or potential conflicts of interest?
     None known

14   Collaborators
     Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not
     listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15   Review question(s)
     State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
     Determine the impact of interventions implemented in health settings in: i) improving screening of patients for
     psychosocial distress

     and Determine the impact of interventions implemented in health settings in: ii) improving referral of cancer patients
     who screen positive on a measure of distress for further assessment and/or psychosocial support

     The secondary aims of the review are to:i) Describe the effectiveness of such interventions on reducing cancer
     patient psychosocial distress

     The secondary aims of the review are to:ii) Describe any unintended adverse effects of such intervention

16   Searches
     Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search
     strategy is not required, but may be supplied as a link or attachment.
     Electronic databases The following electronic databases will be searched for potentially eligible studies; the Cochrane

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Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The MEDLINE search strategy will be adapted for other databases and will include filters used in other systematic reviews for population (cancer patients), screening for distress and referral and psychosocial support. Other sources Studies will also be obtained from the following sources: • Reference lists of included studies • Manual searching of 3 relevant journals in the field (published in the last 5 years); Journal of the National Comprehensive Cancer Network, Psychooncology and Supportive Care in Cancer • Manual searching of conference abstracts published in the preceding 2 years from the International Psycho-Oncology Society and the Society of Behavioural Medicine • A grey literature search using Google Scholar (published online in the last 5 years – the first 200 citations will be examined) Any trials without parallel comparison or control groups will be excluded. There will be no restriction based on length of follow-up. There will be no restrictions based on year of study publication or language. Only studies published in peer reviewed scientific journals will be included.

17   URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18   Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
It is estimated that 35%–40% of cancer patients experience distress at some stage during their illness. Distress may affect cancer patients' functioning, capacity to cope, treatment compliance, quality of life and survival. Best practice clinical guidelines recommend routine psychosocial distress screening and referral to psychosocial supports for cancer patients.

19   Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Participants could include: i) Adult cancer patients who are about to undergo, are currently undergoing or have undergone medical treatment; including radiotherapy, chemotherapy, surgery or combined modality ii) Clinical staff members such as physicians, surgeons, and oncologists, nurses, and allied health professionals responsible for the care of cancer patients at any stage of treatment within primary and secondary health care settings such as hospitals, general practices or oncology clinics. iii) Administrative staff of health services including hospital managers and quality assurance staff responsible for improving the delivery of health services to cancer patients; government or non-government cancer services or other organisations that may influence screening and referral of cancer patients. Studies which examine screening for psychosocial distress and/or referral for psychosocial support for carers of patients with cancer, or survivors of cancer, will be excluded. Studies reporting on cancer patients under the age of 18 will be excluded.

20   Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Types of Interventions Interventions will be included that are implemented in a health setting that aim to improve the rate of routine screening procedures for psychosocial distress and/or referral for psychosocial support in health care settings. Interventions could include quality improvement initiatives, education and training, performance feedback, prompts and reminders, implementation resources, financial incentives or the use of opinion leaders. Interventions could be singular or multicomponent. Consistent with the definition of distress provided by the National Cancer Network psychosocial distress will include any form of experienced distress, which may be due to emotional, psychological, social or spiritual factors. For the purposes of the review, distress screening is defined as the standardised brief assessment of patients to determine whether referral for more extensive assessment and/or psychosocial support services is warranted. Trials of interventions to improve the use of standardised screening tools or instruments with or without additional clinical judgement will be included. Studies using clinical judgement of psychosocial distress alone, without use of a formal screening tool will be excluded. Screening instruments could include traditional measures of psychosocial distress such as the Distress Thermometer [1], patient reported outcome measures of psychological distress including depression and anxiety, for example, the Hospital Anxiety and Depression Scale [29] and measures of health related quality of life (HRQoL) that include a psychological distress component as a core component domain, for example, the MOS 36-Item Short-Form Health Survey. Administration of the screening instrument may be completed orally or via a paper-based questionnaire or computer/tablet questionnaire. Referral for psychosocial support will include any written or verbal offer or direction of a patient for

_____

APPENDIX A5: PRISMA checklist   A   45

further review, consultation, assessment or treatment with any health professional including the primary oncology team or health service offering psychosocial support such as psycho-oncology services. Referral must be made as part of the implemented intervention and based on the results of a distress screening instrument. The referral should not be based on clinical judgement alone. Studies will be included if they implement either distress screening only or distress screening and appropriate referral. Interventions targeting a range of clinical practices such as treatment or management decisions, or medication prescription that also include screening for psychosocial distress and/or referral for appropriate psychosocial support will be included only when data for changes in screening and/or referral is reported separately from other outcomes. Studies where research staff conduct screening or referral will be excluded, as will trials of population-based community screening programmes. Exclusion criteria Studies using clinical judgement of psychosocial distress alone, without use of a formal screening tool will be excluded. Studies where research staff conduct screening or referral will be excluded, as will trial of population-based community screening programmes.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Comparisons will be included that are non intervention controls, 'usual' practice, or that are alternative interventions.

22 Types of study to be included
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Studies with the following study designs will be included: • randomised controlled trials, including cluster randomised controlled trials; • staggered enrolment trials or stepped-wedged trials; • quasi-randomised trials • quasi-experimental trials with comparison/control groups, including non-randomised pre-post (before-after) trials with one or more intervention and control groups, time-series/interrupted time-series trials (including multiple baseline trials) with independent control groups, preference trials and regression discontinuity trials; • historical control studies; • natural experiment studies that have a comparison group. Any trials without comparison or control groups will be excluded. There will be no restriction based on length of follow-up. There will be no restrictions based on year of study publication or language. Only studies published in peer reviewed scientific journals will be included.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)
Give the most important outcomes.
i) Any outcome measure reporting the provision of screening for psychosocial distress will be included (e.g. number or % of cancer patients screened). Such data may be obtained from medical record audits, client or clinician report, administrative data, audio recording or other sources. ii) and/or any outcome measure of the provision of referral for further assessment and/or psychosocial support (e.g. number or % of cancer patients referred). Such data may be obtained from medical record audits, client or clinician report, administrative data, audio recording or other sources such as records of referral service use by organisations providing psychosocial care for cancer patients.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
i) Any validated outcome measure psychosocial distress in the patients (e.g. distress outcome assessments such as the Kessler Psychological Distress Scale) will be included. ii) Any outcome measure of unintended adverse effects or barriers of the intervention to patients, clinicians or health services such as stress in health professionals providing psychosocial screening and referral

Give information on timing and effect measures, as appropriate.

26 Data extraction (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Study selection The titles and abstracts retrieved by electronic searches will be exported to a reference management database (Endnote version X6) to remove duplicates. Two reviewers will independently screen abstracts and titles.

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The reviewers will not be blind to the author or journal information. Screening of studies will be conducted using a standardised screening tool and will be pilot tested with a sample of articles before use. The abstracts of papers that are in a language other than English will be translated using Google Translate. If considered eligible or eligibility is unclear, professional translation of the full paper with be undertaken. The full texts of manuscripts will be obtained for all potentially eligible trials for further examination. For all manuscripts, the primary reason for exclusion will be recorded and documented in the excluded studies table. Discrepancies between the two review authors regarding study eligibility will be resolved by discussion and consensus and if necessary, a third reviewer. Data extraction The two review authors will independently extract data from the included trials using a pre-piloted data extraction form that will be developed based on recommendations from the Cochrane Handbook for Systematic Reviews of Interventions [37]. The data extraction form will be piloted before use. Discrepancies between reviewers regarding data extraction will be resolved by discussion and consensus and if necessary, include a third reviewer. Information will be transferred from data extraction forms into statistical software for meta-analyses. Data items The following information will be extracted: • Authors, year and journal • Study eligibility, study design, health care provider type (e.g. nurses), country, health care setting (e.g. oncology clinic) • Patient characteristics and demographics including cancer site, cancer stage, age, sex, cancer treatment type, treatment status (pre/undergoing/post) • Characteristics of the intervention, including the duration, intervention strategies, the theoretical underpinning of the study (if noted in the study), screening instrument • Trial primary and secondary outcomes, including sample size, the data collection method, validity of measures used, any measures of client uptake or use of psychosocial support services following referral, effect size, measures of change in psychosocial distress • Source(s) of research funding and potential conflicts of interest • Number of participants per experimental condition as well as information to allow assessment of risk of study bias Attempts will be made to contact the corresponding authors of included trials in instances where data is unavailable in the published manuscript.

27   Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Two review authors will independently assess the risk of bias of all included trials using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP) for quantitative studies. This tool covers any quantitative study design and includes components of intervention integrity. Any discrepancies will be resolved through discussion. The EPHPP assesses six methodological dimensions: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. These domains are rated on a three-point scale (strong, moderate, weak) according to pre-defined criteria and procedures recommended for tool use, and then given an overall global rating. Those with no weak ratings are given an overall rating of strong, those with one weak rating are given an overall rating of moderate and those with two or more weak ratings across the six domains are given an overall weak rating. Two additional methodological dimensions provided by the tool are intervention integrity and analyses and these will also completed by the reviewers.

28   Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
Summary measures There are a variety of commonly used screening instruments and scoring thresholds for psychosocial distress. As such, it is anticipated that there will be a range of different outcome measures reported across included studies, which may make meta-analysis of the data from these trials inappropriate, in which case, findings of included studies will be presented narratively. However, for the primary outcomes pertaining to provision of screening for distress and/or referral for further assessment and/or psychosocial care, and secondary outcomes, attempts will be made to conduct meta-analysis using data from included trials. For binary outcomes the standard estimation of the odds ratio and a 95% confidence interval will be calculated. For continuous data the mean difference will be calculated where a consistent measure of outcome is used in included trials. Where different continuous measures are used to examine an outcome, the appropriateness of calculating a standardised mean difference will be considered. Authors of included trials will be contacted to provide additional information if any outcome data is unclear or missing. Data synthesis and analysis Meta-analysis will be performed using random effects models where suitable data and homogeneity exist (Isq Isq>75%), heterogeneity will be explored via subgroup analyses according to trial intervention and population characteristics. Funnel plots will be generated by statistical software to enable the assessment of publication bias. Grading the strength of evidence As recommended by the Cochrane Handbook for Systematic Reviews of Interventions, the overall quality of evidence on outcomes will be presented using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach, which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The overall quality of evidence will be rated at four levels: high, moderate, low and very low.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned

Review general information

30 Type and method of review
Select the type of review and the review method from the drop down list.
Intervention, Systematic review

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Australia

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
McCarter K, Britton B, Baker A, et al. Interventions to improve screening and appropriate referral of patients with cancer for distress: systematic review protocol. BMJ Open 2015;5:e008277. doi:10.1136/bmjopen-2015- 008277

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
The findings of this study will be disseminated via peer-reviewed publications and conference presentations.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
distress

screening

referral

cancer

review

APPENDIX A5: PRISMA checklist

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37   Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38   Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39   Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40   Details of final report/publication(s)
This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

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APPENDIX A5: PRISMA checklist for Paper Two

PRISMA-P (preferred reporting items for systematic review and meta-analysis protocols) 2015 checklist: recommended items to address in a systematic review protocol

Section and topic	Item No	Checklist item	Page
Administrative information			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	70
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	71
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Appendix A6
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Appendix A6

Amendments		4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	99
Support:				
Sources		5a	Indicate sources of financial or other support for the review	Appendix A6
Sponsor		5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder		5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
Introduction				
Rationale		6	Describe the rationale for the review in the context of what is already known	92
Objectives		7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	93
Methods				

Item	No.	Description	Page
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	94
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	96
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Appendix A7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	80
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	79

Section	No.	Description	Page
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	80
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	80
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	77
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	81
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	81
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and	82

Section/topic	#	Checklist item	Page
		methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	82
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	82
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	81
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	83

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Interventions to improve screening and appropriate referral of patients with cancer for distress: systematic review protocol

Kristen McCarter,[1] Ben Britton,[2] Amanda Baker,[2] Sean Halpin,[1] Alison Beck,[2] Gregory Carter,[2] Chris Wratten,[3] Judy Bauer,[4] Debbie Booth,[5] Erin Forbes,[2] Luke Wolfenden[6]

ABSTRACT

Introduction: It is estimated that 35–40% of patients with cancer experience distress at some stage during their illness. Distress may affect functioning, capacity to cope, treatment compliance, quality of life and survival of patients with cancer. Best practice clinical guidelines recommend routine psychosocial distress screening and referral for further assessment and/or psychosocial support for patients with cancer. However, evidence suggests this care is not provided consistently.

Methods and analysis: We developed our methods following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement. The review is registered with PROSPERO and any amendments to the protocol will be tracked. The primary aim of this systematic review is to examine the impact of interventions delivered in healthcare settings that are aimed at (1) improving routine screening of patients for psychosocial distress and (2) referral of distressed patients with cancer for further assessment and/or psychosocial support. The effectiveness of such interventions in reducing psychosocial distress, and any unintended adverse effect of the intervention will also be assessed in patients with cancer. Data sources will include the bibliographic databases Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. Eligible studies must compare an intervention (or two or more interventions) in a healthcare setting to improve the rate of screening for psychosocial distress and/or referral for further assessment and/or psychosocial support for patients with cancer with no intervention or 'usual' practice. Two investigators will independently review titles and abstracts, followed by full article reviews and data extraction. Disagreements will be resolved by consensus and if necessary, a third reviewer. Where studies are sufficiently homogenous, trial data will be pooled and meta-analyses performed.

Ethics and dissemination: No ethical issues are foreseen. The findings of this study will be disseminated widely via peer-reviewed publications and conference presentations.

INTRODUCTION
Rationale
Between 35% and 40% of patients with cancer experience distress at some stage during their illness.[1] Despite this, distress is often unrecognised in patients with cancer by clinicians.[2] Psychological distress can arise in response to cancer-related factors such as diagnosis and cancer progression.[2] Distress may affect functioning, capacity to cope, treatment compliance, quality of life and survival of patients with cancer,[1,3] and increase the treatment burden to the medical team and healthcare system.[4] Addressing distress in cancer populations is, therefore, an important health priority.

The importance of psychosocial care for patients with cancer is recognised by professional associations and is included in clinical guidelines.[5,6] The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Distress Management,[1] and the National Institute for Clinical Excellence guidance manual, Improving Supportive and Palliative Care for Adults with Cancer[7] recommend routine screening for psychosocial distress and subsequent assessment or referral to appropriate services by those responsible for the care of patients with cancer. The Institute of Medicine report, Care for the Whole Patient recommends screening for distress and the development of a treatment plan with referrals as needed to psychosocial services.[8] In 2015, the American College of Surgeons Commission on Cancer will require cancer centres to implement screening programmes for psychosocial distress as a new criterion for

accreditation.[9] Systematic reviews and meta-analyses on which these recommendations are based have demonstrated distress screening and referral improves the identification and management of psychosocial distress and reduces psychological morbidity in patients with cancer.[3 10]

Despite evidence-based guideline recommendations, screening and referral of patients with cancer for psychosocial distress is not routinely conducted by clinicians responsible for the clinical management of patients with cancer.[1 11] While previous reviews of interventions have examined the effects of common distress screening tools, for example, the Distress Thermometer[1] on patients with cancer outcomes such as quality of life or depression,[12–16] or the impact of patient-reported outcome measures to improve identification of distressed patients and improve treatment decisions,[17 18] we are not aware of any previous systematic review of interventions to improve clinician provision of screening and appropriate referral of patients with cancer per se. Reviews of clinical practice changes in interventions more broadly suggest that a range of interventions may be effective in improving clinicians' provision of care consistent with guidelines recommendations such as educational strategies, audit and feedback, use of reminders and multiprofessional collaboration.[19–21]

Objectives

In the absence of reviews particularly aimed at interventions to increase screening and referral for distress in patients with cancer, the primary aims of this review are to determine the impact of interventions to improve clinician provision of screening and appropriate referral of patients with cancer for distress. In particular, we will assess the impact of such interventions on:

1. Improving screening of patients for psychosocial distress;
2. Improving referral of patients with cancer who screen positive on a measure of distress for further assessment and/or psychosocial support.

The secondary aims of the review are to:

1. Describe the effectiveness of such interventions on reducing psychosocial distress of patients with cancer;
2. Describe any unintended adverse effects of such an intervention.

METHODS AND ANALYSIS

The review methods are based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement.[22]

Eligibility criteria
Study characteristics
Types of studies
Inclusion criteria
Studies with the following study designs will be included:

▶ Randomised controlled trials, including cluster randomised controlled trials;
▶ Staggered enrolment trials or stepped-wedged trials;

▶ Quasi-randomised trials;
▶ Quasi-experimental trials with comparison/control groups, including non-randomised pre–post (before–after) trials with one or more intervention and control groups, time-series/interrupted time-series trials (including multiple baseline trials) with independent control groups, preference trials and regression discontinuity trials;
▶ Natural experiment studies that have a comparison group.

Any trial without parallel comparison or control groups will be excluded. There will be no restriction based on length of follow-up. There will be no restrictions based on the year of the study publication or language. Only studies published in peer-reviewed scientific journals will be included.

Participants
Inclusion criteria
Participants could include:

1. Adult patients with cancer who are about to undergo, are currently undergoing or have undergone medical treatment, including radiotherapy, chemotherapy, surgery or combined modality;
2. Clinical staff members such as physicians, surgeons and oncologists, nurses, and allied health professionals responsible for the care of patients with cancer at any stage of treatment within primary and secondary healthcare settings such as hospitals, general practices or oncology clinics;
3. Administrative staff of health services including hospital managers and quality assurance staff responsible for improving the delivery of health services to patients with cancer; government or non-government cancer services or other organisations that may influence screening and referral of patients with cancer.

Exclusion criteria

Studies which examine screening for psychosocial distress and/or referral for appropriate psychosocial support for carers of patients with cancer or survivors of cancer will be excluded. Studies reporting on patients with cancer under the age of 18 will be excluded.

Types of interventions
Inclusion criteria
Interventions will be included that are implemented in a health setting that aim to improve the rate of routine screening procedures for psychosocial distress and/or referral for appropriate psychosocial support in healthcare settings. Interventions could include quality improvement initiatives, education and training,[23–25] performance feedback, prompts and reminders,[19] implementation resources,[26] financial incentives[27] or the use of opinion leaders.[23 28] Interventions could be singular or multicomponent.

Consistent with the definition of distress provided by the National Cancer Network,[1] psychosocial distress will

include any form of experienced distress, which may be due to emotional, psychological, social or spiritual factors. For the purposes of the review, distress screening is defined as the standardised brief assessment of patients to determine whether referral for more extensive assessment and/or psychosocial support services is warranted. Trials of interventions to improve the use of standardised screening tools or instruments with or without additional clinical judgement will be included. Studies using clinical judgement of psychosocial distress alone, without use of a formal screening tool, will be excluded. Screening instruments could include traditional measures of psychosocial distress such as the Distress Thermometer,[1] patient-reported outcome measures of psychological distress including depression and anxiety, for example, the Hospital Anxiety and Depression Scale,[29] and measures of health-related quality of life (HRQoL) that include a psychological distress component as a core component domain, for example, the MOS 36-Item Short-Form Health Survey.[30] Administration of the screening instrument may be completed orally or via a paper-based questionnaire or computer/tablet questionnaire.

Referral for psychosocial support will include any written or verbal offer or direction of a patient for further review, consultation, assessment or treatment with any health professional, including the primary oncology team or health service offering psychosocial support such as psychooncology services. Referral must be made as part of the implemented intervention and based on the results of a distress-screening instrument. The referral should not be based on clinical judgement alone.

Studies will be included if these implement either distress screening only or distress screening and appropriate referral. Interventions targeting a range of clinical practices, such as treatment or management decisions or medication prescriptions that also include screening for psychosocial distress and/or referral for appropriate psychosocial support will be included only when data for changes in screening and/or referral is reported separately from other outcomes. Studies where research staff conduct the screening or referral will be excluded, as will trials of population-based community screening programmes.

Exclusion criteria
Studies using clinical judgement of psychosocial distress alone, without use of a formal screening tool, will be excluded. Studies where research staff conduct the screening or referral will be excluded, as will trial of population-based community screening programmes.

Comparisons
Comparisons will be included that are non intervention controls, 'usual' practice or that are alternative interventions.

Outcomes
Primary outcomes:
1. Any outcome measure reporting the provision of screening for psychosocial distress will be included (eg, number or per cent of patients with cancer screened); such data may be obtained from medical record audits, client or clinician report, administrative data, audio recording or other sources;
2. And/or any outcome measure of the provision of referral for further assessment and/or psychosocial support (eg, number or per cent of patients with cancer referred); such data may be obtained from medical record audits, client or clinician report, administrative data, audio recording or other sources such as records of referral service use by organisations providing psychosocial care for patients with cancer.

Secondary outcomes:
1. Any validated outcome measure of psychosocial distress in the patients (eg, distress outcome assessments such as the Kessler Psychological Distress Scale) will be included;[31]
2. Any outcome measure of unintended adverse effects or barriers of the intervention to patients, clinicians or health services such as stress in health professionals providing psychosocial screening and referral.[32]

Information sources
Electronic databases
The following electronic databases will be searched for potentially eligible studies; the Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The MEDLINE search strategy below will be adapted for other databases and will include filters used in other systematic reviews for population (patients with cancer),[33] screening for distress[34] and referral,[35] and psychosocial support.[36]

Other sources
Studies will also be obtained from the following sources:
▶ Reference lists of included studies;
▶ Manual searching of three relevant journals in the field (published in the past 5 years): *Journal of the National Comprehensive Cancer Network*, *Psychooncology* and *Supportive Care* in Cancer;
▶ Manual searching of conference abstracts published in the preceding 2 years from the International Psycho-Oncology Society and the Society of Behavioural Medicine;
▶ A grey literature search using Google Scholar (published online in the past 5 years—the first 200 citations will be examined).

Search strategy
The search strategy for MEDLINE is in online supplementary appendix 1. This strategy will be adapted to the

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other electronic databases, with any modifications reported in the review manuscript.

Study selection

The titles and abstracts retrieved by electronic searches will be exported to a reference management database (Endnote version X6) to remove duplicates. Two reviewers will independently screen abstracts and titles. The reviewers will not be blind to the author or journal information. Screening of studies will be conducted using a standardised screening tool and will be pilot tested with a sample of articles before use. The abstracts of papers that are in a language other than English will be translated using Google Translate. If considered eligible or eligibility is unclear, professional translation of the full paper will be undertaken.

The full texts of manuscripts will be obtained for all potentially eligible trials for further examination. For all manuscripts, the primary reason for exclusion will be recorded and documented in the excluded studies table. Discrepancies between the two review authors regarding study eligibility will be resolved by discussion and consensus and if necessary, by a third reviewer.

Data extraction

The two review authors will independently extract data from the included trials using a prepiloted data extraction form that will be developed based on recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions.*[37] The data extraction form will be piloted before use. Discrepancies between reviewers regarding data extraction will be resolved by discussion and consensus, and if necessary, include a third reviewer. Information will be transferred from data extraction forms into statistical software for meta-analyses.

Data items

The following information will be extracted:
- Authors, year and journal;
- Study eligibility, study design, healthcare provider type (eg, nurses), country, healthcare setting (eg, oncology clinic);
- Patient characteristics and demographics, including cancer site, cancer stage, age, sex, cancer treatment type, treatment status (pre/undergoing/post);
- Characteristics of the intervention, including the duration, intervention strategies, the theoretical underpinning of the study (if noted in the study), screening instrument;
- Trial primary and secondary outcomes, including sample size, the data collection method, validity of measures used, any measures of client uptake or use of psychosocial support services following referral, effect size, measures of change in psychosocial distress;
- Source(s) of research funding and potential conflicts of interest;
- Number of participants per experimental condition as well as information to allow assessment of risk of study bias.

Attempts will be made to contact the corresponding authors of included trials in instances where data is unavailable in the published manuscript.

Assessment of risk of bias

Two review authors will independently assess the risk of bias of all included trials in accordance with the Cochrane Collaboration's tool in the *Cochrane Handbook for Systematic Review of Interventions.*[37] Disagreement between raters will be resolved by discussion and consensus with the involvement (if necessary) of a third review author. An additional criterion 'potential confounding' will be included for the assessment of the risk of bias in non-randomised trial designs.[37]

Data analysis

Summary measures

There are a variety of commonly used screening instruments and scoring thresholds for psychosocial distress.[34] As such, it is anticipated that there will be a range of different outcome measures reported across included studies, which may make meta-analysis of the data from these trials inappropriate, in which case the findings of included studies will be presented narratively. However, for the primary outcomes pertaining to provision of screening for distress and referral for further assessment and/or psychosocial care, and secondary outcomes, attempts will be made to conduct meta-analysis using data from included trials. For binary outcomes, the standard estimation of the OR and a 95% CI will be calculated. For continuous data, the mean difference will be calculated where a consistent measure of outcome is used in included trials. Where different continuous measures are used to examine an outcome, the appropriateness of calculating a standardised mean difference will be considered. Authors of included trials will be contacted to provide additional information if any outcome data is unclear or missing.

Data synthesis and analysis

Meta-analysis will be performed using random effects models where suitable data and homogeneity exist (I^2 <75%). Clustered trials will be examined for unit of analysis errors. An effective sample size will be calculated for use in meta-analysis for trials with unit of analysis errors without appropriate statistical adjustment. Data will not be pooled for trials of different study designs (e.g, randomised and non-randomised designs). Sensitivity analysis will be performed by removing studies with a high risk of bias and by removing outliers contributing to statistical heterogeneity.

Assessment of study heterogeneity

Heterogeneity will be examined using visual inspection of box plots, forest plots and using the I^2 statistic. Where

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there is evidence of high heterogeneity ($I^2>75\%$), heterogeneity will be explored via subgroup analyses according to trial intervention and population characteristics. Funnel plots will be generated by statistical software to enable the assessment of publication bias.

Grading the strength of evidence

As recommended by the *Cochrane Handbook for Systematic Reviews of Interventions*,[37] the overall quality of evidence on outcomes will be presented using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) approach, which involves consideration of within-study risk of bias (methodological quality), directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias. The overall quality of evidence will be rated at four levels: high, moderate, low and very low.

ETHICS AND DISSEMINATION

The findings of this study will be disseminated via peer-reviewed publications and conference presentations. As no primary data collection will be undertaken, no additional formal ethical assessment and informed consent are required.

DISCUSSION

Despite guideline recommendations for psychosocial distress screening and referral in cancer, research suggests this care is not provided consistently.[2 38] Presently, the effectiveness of interventions aimed at improving clinicians' provision of routine screening and referral for further assessment and/or treatment for psychosocial distress in patients with cancer remains unclear. The conclusions drawn from the present review when disseminated to policymakers, healthcare providers, and researchers will be helpful in identifying effective approaches for designing interventions aimed to improve the rate of routine provision of this cancer care.

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These include:

Supplementary Material	Supplementary material can be found at: **http://bmjopen.bmj.com/content/suppl/2015/09/21/bmjopen-2015-008277.DC1**
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Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections	Articles on similar topics can be found in the following collections Evidence based practice (698) Mental health (656) Oncology (399)

Notes

APPENDIX A7: Search strategy for Paper Two and Paper Three

1. cancer*.mp.

2. exp Neoplasms/

3. tumo?r*.mp.

4. malignan*.mp.

5. exp Adenocarcinoma/

6. exp Leukemia/

7. leukaemia*.mp.

8. metastat*.mp.

9. exp Carcinoma/

10. exp Medical Oncology/

11. exp Sarcoma/

12. choriocarcinoma*.mp.

13. lymphoma*.mp.

14. teratoma*.mp.

15. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14

16. screen*.mp.

17. measure*.mp.

18. assess*.mp.

19. Questionnaires/

20. Diagnosis/

21. instrument.mp.

22. validat*.mp.

23. 16 or 17 or 18 or 19 or 20 or 21 or 22

24. distress*.mp.

25. Stress, Psychological/

1

26. Anxiety/ or exp Anxiety Disorders/

27. Depression/

28. depress*.mp.

29. exp Depressive Disorder/

30. Dysthymic Disorder/

31. Adjustment Disorders/

32. "Quality of Life"/

33. psychosocial.mp.

34. Depressive Disorder, Major/

35. 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34

36. (psychosocial adj3 (care* or support* or service*)).mp.

37. Counseling/

38. (psychological adj3 (support* or care* or service* or therap* or intervention*)).mp.

39. exp Psychotherapy/

40. Mental Health Services/

41. (psycho oncology or psychooncology).mp.

42. Supportive care.mp.

43. Support service*.mp.

44. Social Support/

45. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44

46. Intervention Studies/

47. implement*.mp.

48. disseminat*.mp.

49. adopt*.mp.

50. practice*.mp.

2

51. organi?ational change*.mp.

52. diffusion.mp.

53. system* change*.mp.

54. quality improvement*.mp.

55. transform*.mp.

56. translat*.mp.

57. transfer*.mp.

58. uptake*.mp.

59. sustainab*.mp.

60. institutionali*.mp.

61. routin*.mp.

62. maintenance.mp.

63. capacity.mp.

64. incorporat*.mp.

65. adher*.mp.

66. program*.mp.

67. integrat*.mp.

68. scal*.mp.

69. Randomized Controlled Trial/

70. Non randomized controlled trial*.mp.

71. Random Allocation/

72. Evaluation Studies/

73. Pilot study.mp. or Pilot Projects/

74. Evaluation Studies as Topic/

75. Cohort Studies/

3

76. Controlled Before-After Studies/

77. Historically Controlled Study/

78. Cross-Sectional Studies/

79. (intervention$ adj5 stud$).mp.

80. feasibility pilot*.mp.

81. sequential cohort.mp.

82. Interrupted-time-series stud*.mp.

83. case series.mp.

84. program*.mp.

85. intervention*.mp.

86. Random*.ab.

87. exp clinical trial/

88. trial.ab.

89. double blind.ab.

90. single blind.ab.

91. experiment*.mp.

92. (pretest or pre test).mp.

93. (posttest or post test).mp.

94. (pre post or prepost).mp.

95. Before after.mp.

96. (Quasi-randomised or quasi-randomized or quasi-randomized or quazi-randomised).mp.

97. stepped wedge.mp.

98. Comprehensive cohort.mp.

99. Natural experiment.mp.

4

100. (Quasi experiment or quazi experiments).mp.

101. (Randomised encouragement trial or randomized encouragement trial).mp.

102. (Staggered enrolment trial or staggered enrollment trial).mp.

103. (Nonrandomised or non randomised or nonrandomized or non randomized).mp.

104. Interrupted time series.mp.

105. (Time series and trial).mp.

106. Multiple baseline.mp.

107. 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 6 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106

108. 15 and 23 and 35 and 45 and 107

109. psychology.mp. or Psychology/

110. social work*.mp.

111. 45 or 109 or 110

112. 15 and 23 and 35 and 107 and 111

5

APPENDIX A8: Quality assessment tool for quantitative studies

**QUALITY ASSESSMENT TOOL FOR
QUANTITATIVE STUDIES**

COMPONENT RATINGS

A) SELECTION BIAS

(Q1) **Are the individuals selected to participate in the study likely to be representative of the target population?**
1 Very likely
2 Somewhat likely
3 Not likely
4 Can't tell

(Q2) **What percentage of selected individuals agreed to participate?**
1 80 - 100% agreement
2 60 – 79% agreement
3 less than 60% agreement
4 Not applicable
5 Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

B) STUDY DESIGN

Indicate the study design
1 Randomized controlled trial
2 Controlled clinical trial
3 Cohort analytic (two group pre + post)
4 Case-control
5 Cohort (one group pre + post (before and after))
6 Interrupted time series
7 Other specify _____
8 Can't tell

Was the study described as randomized? If NO, go to Component C.
No   Yes

If Yes, was the method of randomization described? (See dictionary)
No   Yes

If Yes, was the method appropriate? (See dictionary)
No   Yes

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

1

C) CONFOUNDERS

(Q1) Were there important differences between groups prior to the intervention?
    1   Yes
    2   No
    3   Can't tell

The following are examples of confounders:
    1   Race
    2   Sex
    3   Marital status/family
    4   Age
    5   SES (income or class)
    6   Education
    7   Health status
    8   Pre-intervention score on outcome measure

(Q2) If yes, indicate the percentage of relevant confounders that were controlled (either in the design (e.g. stratification, matching) or analysis)?
    1   80 – 100% (most)
    2   60 – 79% (some)
    3   Less than 60% (few or none)
    4   Can't Tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

D) BLINDING

(Q1) Was (were) the outcome assessor(s) aware of the intervention or exposure status of participants?
    1   Yes
    2   No
    3   Can't tell

(Q2) Were the study participants aware of the research question?
    1   Yes
    2   No
    3   Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

E) DATA COLLECTION METHODS

(Q1) Were data collection tools shown to be valid?
    1   Yes
    2   No
    3   Can't tell

(Q2) Were data collection tools shown to be reliable?
    1   Yes
    2   No
    3   Can't tell

RATE THIS SECTION	STRONG	MODERATE	WEAK
See dictionary	1	2	3

APPENDIX A8: Quality assessment tool for quantitative studies   A 68

F) WITHDRAWALS AND DROP-OUTS

(Q1) **Were withdrawals and drop-outs reported in terms of numbers and/or reasons per group?**
  1 Yes
  2 No
  3 Can't tell
  4 Not Applicable (i.e. one time surveys or interviews)

(Q2) **Indicate the percentage of participants completing the study. (If the percentage differs by groups, record the lowest).**
  1 80 -100%
  2 60 - 79%
  3 less than 60%
  4 Can't tell
  5 Not Applicable (i.e. Retrospective case-control)

RATE THIS SECTION	STRONG	MODERATE	WEAK	
See dictionary	1	2	3	Not Applicable

G) **INTERVENTION INTEGRITY**

(Q1) **What percentage of participants received the allocated intervention or exposure of interest?**
  1 80 -100%
  2 60 - 79%
  3 less than 60%
  4 Can't tell

(Q2) **Was the consistency of the intervention measured?**
  1 Yes
  2 No
  3 Can't tell

(Q3) **Is it likely that subjects received an unintended intervention (contamination or co-intervention) that may influence the results?**
  4 Yes
  5 No
  6 Can't tell

H) **ANALYSES**

(Q1) **Indicate the unit of allocation (circle one)**
  community   organization/institution   practice/office   individual

(Q2) **Indicate the unit of analysis (circle one)**
  community   organization/institution   practice/office   individual

(Q3) **Are the statistical methods appropriate for the study design?**
  1 Yes
  2 No
  3 Can't tell

(Q4) **Is the analysis performed by intervention allocation status (i.e. intention to treat) rather than the actual intervention received?**
  1 Yes
  2 No
  3 Can't tell

3

APPENDIX A8: Quality assessment tool for quantitative studies   A   69

GLOBAL RATING

COMPONENT RATINGS
Please transcribe the information from the gray boxes on pages 1-4 onto this page. See dictionary on how to rate this section.

A	SELECTION BIAS	STRONG	MODERATE	WEAK	
		1	2	3	
B	STUDY DESIGN	STRONG	MODERATE	WEAK	
		1	2	3	
C	CONFOUNDERS	STRONG	MODERATE	WEAK	
		1	2	3	
D	BLINDING	STRONG	MODERATE	WEAK	
		1	2	3	
E	DATA COLLECTION METHOD	STRONG	MODERATE	WEAK	
		1	2	3	
F	WITHDRAWALS AND DROPOUTS	STRONG	MODERATE	WEAK	
		1	2	3	Not Applicable

GLOBAL RATING FOR THIS PAPER (circle one):

1	STRONG	(no WEAK ratings)
2	MODERATE	(one WEAK rating)
3	WEAK	(two or more WEAK ratings)

With both reviewers discussing the ratings:

Is there a discrepancy between the two reviewers with respect to the component (A-F) ratings?

No   Yes

If yes, indicate the reason for the discrepancy

1	Oversight
2	Differences in interpretation of criteria
3	Differences in interpretation of study

Final decision of both reviewers (circle one):   **1   STRONG**
                                                        2   MODERATE
                                                        3   WEAK

APPENDIX A8: Quality assessment tool for quantitative studies   A   70

APPENDIX A9: Quality assessment tool for quantitative studies dictionary

Quality Assessment Tool for Quantitative Studies Dictionary

The purpose of this dictionary is to describe items in the tool thereby assisting raters to score study quality. Due to under-reporting or lack of clarity in the primary study, raters will need to make judgements about the extent that bias may be present. When making judgements about each component, raters should form their opinion based upon information contained in the study rather than making inferences about what the authors intended.

A) SELECTION BIAS

(Q1) Participants are more likely to be representative of the target population if they are randomly selected from a comprehensive list of individuals in the target population (score very likely). They may not be representative if they are referred from a source (e.g. clinic) in a systematic manner (score somewhat likely) or self-referred (score not likely).

(Q2) Refers to the % of subjects in the control and intervention groups that agreed to participate in the study before they were assigned to intervention or control groups.

B) STUDY DESIGN

In this section, raters assess the likelihood of bias due to the allocation process in an experimental study. For observational studies, raters assess the extent that assessments of exposure and outcome are likely to be independent. Generally, the type of design is a good indicator of the extent of bias. In stronger designs, an equivalent control group is present and the allocation process is such that the investigators are unable to predict the sequence.

Randomized Controlled Trial (RCT)
An experimental design where investigators randomly allocate eligible people to an intervention or control group. A rater should describe a study as an RCT if the randomization sequence allows each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. If the investigators do not describe the allocation process and only use the words 'random' or 'randomly', the study is described as a controlled clinical trial.

See below for more details.

Was the study described as randomized?

Score YES, if the authors used words such as random allocation, randomly assigned, and random assignment.

Score NO, if no mention of randomization is made.

Was the method of randomization described?

Score YES, if the authors describe any method used to generate a random allocation sequence.

Score NO, if the authors do not describe the allocation method or describe methods of allocation such as alternation, case record numbers, dates of birth, day of the week, and any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers of assignments.
If NO is scored, then the study is a controlled clinical trial.

Was the method appropriate?

Score YES, if the randomization sequence allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which intervention was next. Examples of appropriate approaches include assignment of subjects by a central office unaware of subject characteristics, or sequentially numbered, sealed, opaque envelopes.

Score NO, if the randomization sequence is open to the individuals responsible for recruiting and allocating participants or providing the intervention, since those individuals can influence the allocation process, either knowingly or unknowingly.

If NO is scored, then the study is a controlled clinical trial.

Controlled Clinical Trial (CCT)
An experimental study design where the method of allocating study subjects to intervention or control groups is open to individuals responsible for recruiting subjects or providing the intervention. The method of allocation is transparent before assignment, e.g. an open list of random numbers or allocation by date of birth, etc.

Cohort analytic (two group pre and post)
An observational study design where groups are assembled according to whether or not exposure to the intervention has occurred. Exposure to the intervention is not under the control of the investigators. Study groups might be non-equivalent or not comparable on some feature that affects outcome.

Case control study
A retrospective study design where the investigators gather 'cases' of people who already have the outcome of interest and 'controls' who do not. Both groups are then questioned or their records examined about whether they received the intervention exposure of interest.

Cohort (one group pre + post (before and after)
The same group is pretested, given an intervention, and tested immediately after the intervention. The intervention group, by means of the pretest, act as their own control group.

Interrupted time series
A time series consists of multiple observations over time. Observations can be on the same units (e.g. individuals over time) or on different but similar units (e.g. student achievement scores for particular grade and school). Interrupted time series analysis requires knowing the specific point in the series when an intervention occurred.

C)   CONFOUNDERS

By definition, a confounder is a variable that is associated with the intervention or exposure and causally related to the outcome of interest. Even in a robust study design, groups may not be balanced with respect to important variables prior to the intervention. The authors should indicate if confounders were controlled in the design (by stratification or matching) or in the analysis. If the allocation to intervention and control groups is randomized, the authors must report that the groups were balanced at baseline with respect to confounders (either in the text or a table).

D)   BLINDING

(Q1) Assessors should be described as blinded to which participants were in the control and intervention groups. The purpose of blinding the outcome assessors (who might also be the care providers) is to protect against detection bias.

(Q2) Study participants should not be aware of (i.e. blinded to) the research question. The purpose of blinding the participants is to protect against reporting bias.

E) DATA COLLECTION METHODS

Tools for primary outcome measures must be described as reliable and valid. If 'face' validity or 'content' validity has been demonstrated, this is acceptable. Some sources from which data may be collected are described below:

<u>Self reported data</u> includes data that is collected from participants in the study (e.g. completing a questionnaire, survey, answering questions during an interview, etc.).

<u>Assessment/Screening</u> includes objective data that is retrieved by the researchers. (e.g. observations by investigators).

<u>Medical Records/Vital Statistics</u> refers to the types of formal records used for the extraction of the data.

Reliability and validity can be reported in the study or in a separate study. For example, some standard assessment tools have known reliability and validity.

F) WITHDRAWALS AND DROP-OUTS

Score **YES** if the authors describe BOTH the numbers and reasons for withdrawals and drop-outs.

Score **NO** if either the numbers or reasons for withdrawals and drop-outs are not reported.

The percentage of participants completing the study refers to the % of subjects remaining in the study at the final data collection period in all groups (i.e. control and intervention groups).

G) INTERVENTION INTEGRITY

The number of participants receiving the intended intervention should be noted (consider both frequency and intensity). For example, the authors may have reported that at least 80 percent of the participants received the complete intervention. The authors should describe a method of measuring if the intervention was provided to all participants the same way. As well, the authors should indicate if subjects received an unintended intervention that may have influenced the outcomes. For example, co-intervention occurs when the study group receives an additional intervention (other than that intended). In this case, it is possible that the effect of the intervention may be over-estimated. Contamination refers to situations where the control group accidentally receives the study intervention. This could result in an under-estimation of the impact of the intervention.

H) ANALYSIS APPROPRIATE TO QUESTION

Was the quantitative analysis appropriate to the research question being asked?

An intention-to-treat analysis is one in which all the participants in a trial are analyzed according to the intervention to which they were allocated, whether they received it or not. Intention-to-treat analyses are favoured in assessments of effectiveness as they mirror the noncompliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.

Component Ratings of Study:

For each of the six components A – F, use the following descriptions as a roadmap.

A) SELECTION BIAS

Strong: The selected individuals are very likely to be representative of the target population (Q1 is 1) **and** there is greater than 80% participation (Q2 is 1).

Moderate: The selected individuals are at least somewhat likely to be representative of the target population (Q1 is 1 or 2); **and** there is 60 - 79% participation (Q2 is 2). 'Moderate' may also be assigned if Q1 is 1 or 2 and Q2 is 5 (can't tell).

Weak: The selected individuals are not likely to be representative of the target population (Q1 is 3); **or** there is less than 60% participation (Q2 is 3) **or** selection is not described (Q1 is 4); and the level of participation is not described (Q2 is 5).

B) DESIGN

Strong: will be assigned to those articles that described RCTs and CCTs.

Moderate: will be assigned to those that described a cohort analytic study, a case control study, a cohort design, or an interrupted time series.

Weak: will be assigned to those that used any other method or did not state the method used.

C) CONFOUNDERS

Strong: will be assigned to those articles that controlled for at least 80% of relevant confounders (Q1 is 2); **or** (Q2 is 1).

Moderate: will be given to those studies that controlled for 60 – 79% of relevant confounders (Q1 is 1) **and** (Q2 is 2).

Weak: will be assigned when less than 60% of relevant confounders were controlled (Q1 is 1) **and** (Q2 is 3) **or** control of confounders was not described (Q1 is 3) **and** (Q2 is 4).

D) BLINDING

Strong: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **and t**he study participants are not aware of the research question (Q2 is 2).

Moderate: The outcome assessor is not aware of the intervention status of participants (Q1 is 2); **or** the study participants are not aware of the research question (Q2 is 2); **or b**linding is not described (Q1 is 3 and Q2 is 3).

Weak: The outcome assessor is aware of the intervention status of participants (Q1 is 1); **and** the study participants are aware of the research question (Q2 is 1).

E) DATA COLLECTION METHODS

Strong: The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have been shown to be reliable (Q2 is 1).

Moderate: The data collection tools have been shown to be valid (Q1 is 1); **and** the data collection tools have not been shown to be reliable (Q2 is 2) **or** reliability is not described (Q2 is 3).

Weak: The data collection tools have not been shown to be valid (Q1 is 2) **or** both reliability and validity are not described (Q1 is 3 and Q2 is 3).

F) WITHDRAWALS AND DROP-OUTS - a rating of:

Strong: will be assigned when the follow-up rate is 80% or greater (Q2 is 1).

Moderate: will be assigned when the follow-up rate is 60 – 79% (Q2 is 2) **OR** Q2 is 5 (N/A).

Weak: will be assigned when a follow-up rate is less than 60% (Q2 is 3) or if the withdrawals and drop-outs were not described (Q2 is 4).

Eating As Treatment (EAT) study protocol: a stepped-wedge, randomised controlled trial of a health behaviour change intervention provided by dietitians to improve nutrition in patients with head and neck cancer undergoing radiotherapy

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ABSTRACT

Introduction: Maintaining adequate nutrition for Head and Neck Cancer (HNC) patients is challenging due to both the malignancy and the rigours of radiation treatment. As yet, health behaviour interventions designed to maintain or improve nutrition in patients with HNC have not been evaluated. The proposed trial builds on promising pilot data, and evaluates the effectiveness of a dietitian-delivered health behaviour intervention to reduce malnutrition in patients with HNC undergoing radiotherapy: Eating As Treatment (EAT).

Methods and analysis: A stepped-wedge cluster randomised design will be used. All recruitment hospitals begin in the control condition providing treatment as usual. In a randomly generated order, oncology staff at each hospital will receive 2 days of training in EAT before switching to the intervention condition. Training will be supplemented by ongoing supervision, coaching and a 2-month booster training provided by the research team. EAT is based on established behaviour change counselling methods, including motivational interviewing, cognitive–behavioural therapy, and incorporates clinical practice change theory. It is designed to improve motivation to eat despite a range of barriers (pain, mucositis, nausea, reduced or no saliva, taste changes and appetite loss), and to provide patients with practical behaviour change strategies. EAT will be delivered by dietitians during their usual consultations. 400 patients with HNC (nasopharynx, hypopharynx, oropharynx, oral cavity or larynx), aged 18+, undergoing radiotherapy (>60 Gy) with curative intent, will be recruited from radiotherapy departments at 5 Australian sites. Assessments will be conducted at 4 time points (first and final week of radiotherapy, 4 and 12 weeks postradiotherapy). The primary outcome will be a nutritional status assessment.

Ethics and dissemination: Ethics approval from all relevant bodies has been granted. Study findings will be disseminated widely through peer-reviewed publications and conference presentations.
Trial registration number: ACTRN12613000320752.

INTRODUCTION

Malignancies of the upper aerodigestive tract and its connected structures, known collectively as Head and Neck Cancers (HNC), are the fifth most commonly diagnosed cancers worldwide.[1] HNC has a relatively high mortality rate, approaching 50%.[2] Malnutrition is a major problem for people with HNC. The prevalence of malnutrition across all patients with cancer in Australia has been reported as between 40% and 80%, with patients with HNC over-represented in this figure.[3] The malignancy itself can cause difficulty in eating, fatigue, loss of appetite and weight loss; and treatments for the cancer can compound these problems with mucositis, dry mouth and taste changes.[4]

Impact of malnutrition

The consequences of malnutrition in patients with cancer include impaired immune function, reduced vitality and reduced resistance to the disease, which lead to an increase in complications due to side effects of the treatment and increased morbidity.[5] Further, the effectiveness of the radiotherapy itself is significantly reduced if the

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patient becomes so malnourished they require a break or early termination of treatment.[6] Multiple laboratory and clinical trials have demonstrated that treatment interruption is the strongest predictor of poor radiotherapy outcome,[7] and malnutrition is one of the most common reasons for treatment to be interrupted.[8] Therefore, it is not surprising that poor nutritional status during treatment has been found to be a strong predictor of mortality in HNC.[9] Further, a dose effect of malnutrition has been found, with a greater than 20% weight reduction over the course of treatment resulting in a significant increase in toxicity and mortality during radiation therapy.[10] Given the impact of malnutrition on the health of people with HNC and their response to treatment, it is usual practice for patients to consult regularly with a dietitian throughout the course of their treatment.

Mental illness in head and neck cancer

In addition to nutritional difficulties, patients with HNC also exhibit relatively high rates of mental health problems, particularly depression.[11] Our recent study found that baseline depression predicted those patients with HNC who were most likely to become malnourished by the end of their treatment.[12] Depression was a better predictor than the commonly accepted risk factors for malnutrition: gender, age, presence of a live-in carer, tumour stage, dose of radiation, concurrent chemotherapy or surgery.[12] It has also been suggested that the high levels of disfigurement and loss of functioning in HNC may lead to greater levels of anxiety than those found in other cancer populations.[13] Furthermore, the risk factors for HNC (smoking and alcohol misuse)[14] may be indicative of premorbid depression[15] in these patients, and have been linked to worse treatment side effects[16–19] and poorer outcomes of radiotherapy.[20–23] Despite the high prevalence of mental illness among patients with HNC and the implications for treatment, a recent systematic review reported that no studies have evaluated psychological interventions targeting health behaviours among patients with HNC.[24]

Compliance problems in head and neck cancer

Patient compliance with dietary advice is essential to achieve positive treatment and health outcomes. A systematic review of nutrition advice in patients with HNC receiving radiotherapy found that dietetic intervention throughout treatment maintained or improved patients' nutritional status.[25] Furthermore, nutritional advice has been found to improve a range of patient outcomes during[26] and after treatment,[27] including treatment completion rates, unplanned hospital visits, length of stay and weight loss.[28] However, patients with HNC are often non-compliant with dietary advice. For some, having to return to the hospital for dietetic appointments in addition to their radiotherapy can be an impediment; particularly if the appointments are not viewed as a core component of their cancer treatment.

In response, dietitians often lack the specific confidence, skills and time to change the dietary behaviours of patients with HNC, especially if those patients have mental health and/or substance use problems and may not see dietetic care as important.

Eating as treatment

This trial attempts to address the inherent difficulties in intervening with the HNC population including their premorbid mental health, non-engagement and non-compliance with dietary advice. It does this by providing dietitians with training, skills and knowledge to deal with this difficult and often overlooked group. The study builds on previous findings by employing motivational interviewing (MI[29]), a counselling style shown to be effective among other non-compliant patient groups[30] and simple cognitive and behavioural strategies. Dietitians will be trained, supervised and coached in the provision of the intervention known as Eating As Treatment (EAT), guided by an intervention manual (available on request). Dietitians will also receive training in the administration of a brief screening tool for symptoms of depression. In accordance with best practice recommendations, dietitians will be supported to identify patients at risk of psychosocial distress and to work with the HNC team to mobilise appropriate support. A raft of evidence-based practice-change strategies will also be adopted to overcome systemic and other barriers to clinician compliance, thereby maximising the clinical implementation of EAT.

Aims and hypotheses

This trial aims to test the effectiveness of the EAT intervention. EAT is a dietitian-delivered intervention to prevent malnutrition in patients with HNC undergoing radiotherapy at five Australian hospital sites. The primary objective of the trial is to maintain nutrition in patients with HNC undergoing radiotherapy.

It is hypothesised that patients with HNC receiving the EAT intervention will have lower malnutrition scores, as measured by the Patient-Generated—Subjective Global Assessment (PG-SGA), at post-treatment and follow-up, compared with patients in the control condition (receiving usual care).

Secondary hypotheses are that, relative to control patients, intervention patients will have higher rates of treatment completion, fewer unplanned hospital visits, shorter lengths of stay, lower depression, higher quality of life and more quality adjusted life years.

METHODS AND ANALYSIS
Trial design

The present study utilises a stepped-wedge, cluster-randomised controlled design. In a stepped-wedge design, all recruitment sites (hospitals) begin in the control condition and then move to the intervention condition in a randomised order (figure 1). This design

Figure 1 Progression of intervention roll-out in a stepped-wedge model.

	Initiation	Step 1	Step 2	Step 3	Step 4	Step 5
Adelaide	Control	Intervention	Intervention	Intervention	Intervention	Intervention
Melbourne	Control	Control	Intervention	Intervention	Intervention	Intervention
Sydney	Control	Control	Control	Intervention	Intervention	Intervention
Perth	Control	Control	Control	Control	Intervention	Intervention
Brisbane	Control	Control	Control	Control	Control	Intervention

was chosen because the intervention involves training dietitians and changing their practice, a simple, randomised trial would require the dietitians to ignore the intervention principles and skills they have learned when treating control patients, making the likelihood for contamination very high. Therefore, a cluster-randomised design was necessary. A standard, parallel, cluster-randomised trial would require a large number of hospitals that treat high numbers of patients with HNC. The low number of radiotherapy departments in Australia treating high numbers of patients with HNC meant that this option was also not possible. A stepped-wedge, cluster-randomised, controlled trial provides the same level of evidence as a standard, parallel, cluster-randomised controlled trial[31] using fewer sites, while reducing the potential for contamination.

Recruitment

Sites were recruited through the Trans-Tasman Radiation Oncology Group (TROG) who invited members from large radiotherapy departments within Australian hospitals to put their sites forward as potential clusters. Participants will be recruited from six of these large radiotherapy departments located in Adelaide, South Australia; Melbourne, Victoria; Sydney, New South Wales; Perth, Western Australia; and Brisbane, Queensland. There are two hospitals in Brisbane that share a dietetic department. So, although patients are recruited from two different hospitals, they will be treated as one progression step in the stepped wedge, and move to the intervention period at the same time. This equates to a total of five wedge steps.

Prior to study commencement, the order in which hospitals receive training (thereby the duration of control and intervention periods) was randomised by an independent statistician using a uniform random number generator in STATA. The randomised order was Adelaide, Melbourne, Sydney, Perth and Brisbane.

Participants
Inclusion criteria
Patients eligible for inclusion will meet the following criteria:
▶ Aged 18 years or older.
▶ Pathologically confirmed diagnosis of HNC, that is, cancer involving the nasopharynx, oropharynx, oral cavity, larynx, or hypopharynx, requiring definitive or

postoperative radiotherapy with curative intent (chemoradiation (including neoadjuvant and adjuvant chemotherapy) permitted).
▶ Regional nodal irradiation included in PTV1 (as a minimum ipsilateral levels II-III), and receiving a prescribed dose of at least 60 Gy.
▶ Available for follow-up for at least 6 months poststudy initiation.
▶ Capacity to provide written informed consent.
Exclusion criteria
▶ Inability to communicate in English.
▶ Presence of organic brain diseases (impairing ability to complete questionnaires satisfactorily).
▶ Likely insignificant oral or pharyngeal mucositis as a complication of radiotherapy treatment (patients with T1/T2 glottic carcinoma undergoing small-field radiotherapy or T1/T2 tonsil cancer undergoing unilateral treatment).

Recruitment

Approximately one participant per week per hospital will be expected to be enrolled in the study. It is estimated that at this rate, recruitment will run for approximately 22 months.

Treatment
Control
During the control phase, each hospital will be instructed to deliver treatment as usual, making no changes to any part of their clinical care.

Intervention
Training
When a hospital moves from control to intervention, researchers will travel to the hospital to provide training. This will be delivered in a 2-day workshop followed by a day in which a booster training session is delivered, followed by the researchers accompanying dietitians during their usual consultations to help them integrate into their clinical practice what they have learned. The researchers will return 2 months later to refresh EAT intervention skills, problem-solve clinical concerns, and troubleshoot any practice change issues that may have arisen. During the intervention phase, dietitians will participate in regular supervision with one of the researchers (clinical psychologist, AKB). Where possible, individual supervision via telephone will occur fortnightly

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for the first 2 months post-training, and regular written feedback will be provided. Group supervision will be introduced during the 2-month 'booster' visit. Group supervision will then occur monthly, thereafter, via skype/teleconference/videoconference. Supervision will be used to discuss clinical issues, problem-solve, and provide skills-based feedback. Common themes, barriers and solutions discussed during supervision will be distributed (eg, email/discussion board) to participating dietitians across all hospitals.

Eating as treatment

The intervention is named EAT, to emphasise that maintaining adequate nutrition during radiotherapy is an integral part of cancer treatment and not merely an adjunct to survival. In order for patients with HNC to eat, they must overcome significant barriers of pain, oral disfigurement, mucositis, nausea, reduced or no saliva, taste changes and severe loss of appetite, in addition to the premorbid complications of high rates of smoking, alcohol misuse, mental health problems and poor levels of self-care.

The content of the intervention is a distillation of behaviour change strategies of MI and cognitive–behavioural therapy (CBT), developed specifically for patients with HNC undergoing radiotherapy, and targeting behaviours around nutrition. The intervention was successfully piloted by a clinical psychologist,[12] and has been refined for delivery by dietitians in the clinical setting, alongside their standard dietetic consultations with patients with HNC. The refined training was piloted with dietitians at the Calvary Mater Newcastle, who found the training acceptable, feasible and useful.

Although the training is standardised, the intervention itself is not highly structured, as it has been demonstrated that MI studies that do not have a structured manual produce almost double the effect size of those that are highly manualised.[32] Instead, training in EAT uses simply worded principles to guide the dietitian (figure 2), reminding them to integrate the skills they have learned in training into their normal clinical practice.

The first principle refers to the MI interactional style in which clinicians are empathic, collaborative and elicit motivation for change from the patients themselves.[29] This principle refers both to the importance of allowing the patient reinforce their own reasons for change (change talk), as well as avoiding pushing the patient into creating arguments not to change (sustain talk). These skills will be used to elicit motivation to change eating behaviour and to help generate concrete behavioural goals.

There are no specific 'scripts' in EAT. However, there is one specific conversation that dietitians will be trained to hold with patients, referred to as Eat To Live. Using MI skills, dietitians will elicit patients' reasons for having radiotherapy. Although patients' reasons will be many and varied, ultimately, a core reason for undergoing the rigours of radiotherapy will have some element of wanting to live (palliative treatment is an exclusion

criterion). We can be confident that this is the case, as they are attending radiotherapy every day for 5–7 weeks, despite sometimes quite severe side effects. Dietitians then offer an invitation to explain the correlation between malnutrition during radiotherapy and poorer outcomes. It is important that this information is delivered as a description of the HNC population rather than becoming accusatory of the patient's behaviour personally, thus keeping to the first principle. The dietitian then deploys variance by inviting the patient to reflect on their continued attendance at radiotherapy and their concurrent nutritional behaviours that may not be enhancing the likelihood of meeting the core goal of living. As always, deploying variance requires a good rapport and genuineness for it not to seem accusatory and confrontational. From this point, the dietitian attempts to convert the motivation elicited into concrete dietary behavioural changes by asking the patient what they feel are the next step.

The remaining three principles in EAT will be operationalised in a nutritional planner that the dietitian and patient work on collaboratively. Together, they generate a weekly grid of nutritional behaviours, such as eating breakfast, conducting oral care of ulcers, or drinking a meal replacement supplement. When the patient is happy with the plan, both they and the dietitian sign it, and the dietitian takes a copy and they agree to review it the following week. The patient then ticks each behaviour as they complete it each day. This process makes the behaviours more likely through self-generation,[29] self-monitoring,[33] having a concrete meal plan,[34] tailoring,[35] achievability,[36] reinforcement and accountability;[37] all of which are CBT strategies that have been successful in nutritional behaviour change trials.[38]

Implementation of EAT

The intervention was developed to integrate with the *Evidence Based Practice Guidelines for the Nutritional Management of Adult Patients with Head and Neck Cancer.*[39] While EAT is predominately a style of interaction, in order to maximise potential benefit for patients, it requires that (1) patients receive frequent contact with dietitians to enable sufficient exposure to the intervention; (2) ongoing dietitian's use of a validated nutrition assessment tool to enable the dietitian to present a patient's non-compliance with dietetic advice in a standard, objective, but non-confrontational way and that (3) patients at risk of depression be offered psychosocial support to reduce the risk that depressive symptoms do not hinder patient motivation and capacity to engage with dietitians or action nutritional plans agreed with dietitians during consultation. As such, during the intervention phase, sites receive a range of supportive clinical practice change strategies to facilitate the delivery of the EAT intervention in addition to the provision and/or maintenance of clinical practice guidelines recommendations regarding the frequency of dietitian contact during and after radiotherapy, the use of a validated

Figure 2   Principles prompt and conversation guide for Eating as Treatment.

nutritional assessment tool to assess and monitor nutritional adequacy of patients, and the screening and referral of patients at risk for psychosocial support. Specifically, the research team will provide sites with the following evidence-based, clinical practice change support strategies (box 1).

Executive support and endorsement

Senior trial investigators will solicit the support and endorsement of executive staff from each site for the implementation of the EAT intervention and dietetic

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Box 1   Best practice clinical guidelines for patients with head and neck cancer

Best practice clinical guidelines for patients with head and neck cancer recommend:
▶ ≥125 kJ/kg/day and 1.2 g protein/kg/day
▶ Use of a validated nutritional assessment tool
▶ Dietetic consults weekly, then fortnightly
▶ Screening and referral for distress

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clinical guidelines.[40–42] These trial investigators include clinical psychologists, an implementation scientist, and an expert opinion leader in the field of head and neck dietetic care, and author of the *Evidence-based practice guidelines for the nutritional management of adult patients with head and neck cancer.*[39] Specifically, these members of the research team will meet via teleconference with the department head of dietetics and the principal investigator from the radiotherapy department at each participating site 2 weeks prior to training (described below). These executive site staff will be asked to demonstrate leadership and support for the EAT intervention and clinical guidelines, for example, by communicating their support for the clinical practice change and expectations of staff at the training workshops and throughout the intervention phase of the trial. These staff will also be asked to take responsibility for addressing any barriers to change arising at the executive level.

Provision of staff training

The workshop and booster session (described previously) will seek to enhance staff knowledge, skills and

attitudes toward the EAT intervention and the best practice dietetic guidelines, and address barriers to such care provision identified in the literature. Specific to depression-screening recommendations, dietitians will be trained in a method used to screen for symptoms of depression using the Patient Health Questionnaire-2 (PHQ-2).[43] The PHQ-2 consists of two key screening items from the larger PHQ-9 and has been shown to have good psychometric properties (ROC AUC=0.084) in a radiotherapy outpatients population.[44] It asks the participant to rate the frequency of two major depressive episode criteria over the last 2 weeks from 0 to 3. This provides the clinician with an indication of whether the patient may be at risk of experiencing clinically significant symptoms of depression. Training will combine didactic and interactive components including opportunities for discussion, role play and facilitator-provided feedback. This approach is consistent with recommendations for effective training that facilitates learning.[45 46]

Academic detailing

Clinical psychologists from the research team will attend the radiotherapy department dietetic clinics to 'shadow' dietitians for 1 day following both the 2-day training workshop and the booster training session (2 months after initial training). The research staff will be guided in this process by the use of a checklist that clearly defines the educational and behavioural objectives of the EAT intervention and clinical guidelines. The clinical psychologists will (1) reinforce the essential messages using active dietitian participation, (2) informally assess intervention implementation, (3) help resolve implementation barriers and assist with the integration of systems changes specific to that clinic to support best practice dietetic intervention, (4) provide advice, feedback, support and positive reinforcement of improved practices to dietitians regarding patient care and (5) set explicit targets and develop an action plan with dietitians.[47–49]

Systems and prompts

To facilitate patient attendance for dietetic treatment, services will be encouraged to schedule outpatient appointments adjacent to radiotherapy appointments. Integrating dietetic management into radiotherapy in this way helps to position dietetic intervention and counselling as an integral part of cancer care for both the patients and the department staff. Dietitians will be asked to schedule patient consultations according to the recommendations of the clinical guidelines (weekly during radiotherapy, fortnightly for 6 weeks post-treatment, and 'as required' thereafter). Dietitians will be asked to record dietetic consultations in patient medical records. Consistent with recommendations for effective implementation of clinical guidelines into routine practice, the medical records of participating patients will include a coloured printed prompt, placed by research staff, to remind and guide dietitians in the

key components of the EAT intervention. The PG-SGA and PHQ-2 will also be included in trial patients' records to facilitate standardised nutrition assessment and depression screening as recommended by the clinical guidelines.[50] For services without existing referral pathways for psychosocial support for patients with cancer, the research team will work with the dietitians and radiation oncologist at each site to collaboratively develop a referral policy for those patients screened as at risk for depression.

Performance audit and feedback

Patient medical records and audio recorded patient consultations will be audited regularly by study personnel to assess the provision of the EAT intervention behavioural change techniques and care consistent with the clinical guidelines. Consistent with recommendations for effective feedback and monitoring, feedback regarding site performance data relative to agreed benchmarks will be provided in written and verbal forms at multiple time-points.[48 49] The expert opinion leader in HNC nutritional management and the behavioural scientist from the research team will have regular phone meetings every 3–4 months with the head of the dietetics departments of the intervention sites to provide information about the current level of care provided by staff, relative to best practice guidelines and the EAT intervention. Reports providing aggregated data will be provided to the head of dietetics at each site prior to these calls at 3–4 month intervals after training. With permission of the head of dietetics, these reports will also be sent to site dietetic staff. During these calls, the expert opinion leader will review performance feedback using these reports, identify opportunities for improvement, assist with problem solving, agree on the goals for the next month including performance benchmarks, and set an action plan.[48] The head of dietetics at the intervention site will be encouraged to implement strategies to improve care when it is found to be inconsistent with the EAT intervention components.

Additional support and feedback for the intervention will be provided as part of academic detailing, and through ongoing formal and informal supervision, with a clinical psychologist assisting with the implementation, barriers and maintenance of the system change. As part of these regular meetings, audio tapes of dietetic consultations with trial patients will be discussed. Those clinicians not meeting benchmarks will be encouraged to discuss potential impediments with the clinical psychologist during supervision.

Provision of tools and resources

Given identified barriers to implementation of clinical guidelines including lack of information and clinical uncertainty,[50 51] services and staff will have access to well presented, user friendly EAT intervention manuals and print resources, nutrition assessment tools, depression-screening procedures and psychosocial referral options

that will be provided during training, so as to facilitate discussion and practice.[40 41 52] They will also have access to regular phone and videoconferences with the clinical psychologist and project manager to discuss barriers and solutions to implementation. Barriers to intervention implementation and any necessary resources required for training will be discussed during a teleconference with sites 2 weeks prior to training.

Treatment verification and delivery

Dietitians will be required to audio-record treatment sessions with participants and to use a monitoring form to document the number and frequency of their dietetic consultations.

A random selection of audio tapes pretraining and post-training, will be reviewed by two independent assessors for fidelity to the EAT manual. Fidelity will be assessed using the Behaviour Change Counselling Index,[53 54] a standardised, evidence-based checklist for assessing behaviour change counselling skills. Following the EAT training, additional items will be added to assess the presence of specific components of the EAT intervention.

Assessments

Assessments of primary and secondary outcomes and covariates will be conducted by an independent research officer during the first and last weeks of radiotherapy (typically 6 weeks apart) and follow-up will occur 4 and 12 weeks after the completion of radiotherapy (table 1). As part of routine treatment, the Common Terminology Criteria for Adverse Events,[55] mucositis (oral, pharyngeal

and laryngeal) and dysphagia assessments will also be performed by the radiation oncologist.

Primary outcome: nutritional status

The PG-SGA[56 57] is considered the gold standard in oncology nutrition. The assessment examines known prognostic indicators of nutrition such as weight change, dietary intake, gastrointestinal symptoms, changes in functional capacity, nutritional intake, metabolic stress, subcutaneous fat, muscle wasting, disease and treatment. It consists of a self-report questionnaire and clinical assessment conducted by a member of the study team. Higher scores reflect a higher risk of malnutrition.

Secondary outcomes

Depression: The PHQ-9[43] is a self-administered nine-item questionnaire that assesses depression. Participants are asked to rate (on a scale of 0–3) the frequency of various Major Depressive Episode criteria over the previous 2 weeks. It provides two pieces of information; whether the patient is likely to meet criteria for a major depressive episode, and a measure of the severity of the depression from 0 to 27.

Quality of Life: The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) is a psychometrically validated[58] 30-item self-report questionnaire designed to measure quality of life in patients with cancer. The EORTC QLQ-C30 consists of five functional scales (physical, role, cognitive, emotional and social), three symptom scales (fatigue, pain and nausea and vomiting), a global health status scale, and six single items

Table 1 Schedule of assessment measures

	First week of radiotherapy	Last week of radiotherapy	Four weeks after	Twelve weeks after
Primary outcome				
Nutritional status assessment: PG-SGA	✓	✓	✓	✓
Secondary outcomes				
Depression: PHQ-9	✓	✓	✓	✓
Quality of life: EORTC	✓	✓	✓	✓
Quality adjusted life years: EORTC	✓	✓	✓	✓
Covariates				
Therapeutic alliance: dietitian	✓		✓	✓
ARM-5 (clinician)				
Therapeutic alliance: client	✓		✓	✓
ARM-5 (client)				
Nicotine dependence: FTND	✓		✓	✓
Alcohol dependence: AUDIT	✓			
Alcohol use: AUDIT-consumption	✓		✓	✓
Smoking: biochemical validation expired carbon monoxide	✓		✓	✓
Dysphagia: Australian standard of food texture	✓	✓	✓	✓
Chart audit	✓			✓

ARM-5, Agnew Relationship Measure—Five Item Version; AUDIT, The Alcohol Use Disorders Identification Test; EORTC, European Organisation for Research and Treatment of Cancer; FTND, The Fagerstrom Test for Nicotine Dependence; PG-SGA, Patient Generated Subjective Global Assessment; PHQ-9, The Patient Health Questionnaire 9.

assessing the perceived financial impact of the disease and additional symptoms commonly reported by patients with cancer (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea). Scale and individual item scores range 0–100. Higher scores reflect a higher response level—high functional scores indicate a high/ healthy level of functioning; higher symptom scores reflecting higher symptomatology/problems; higher scores on individual items reflect stronger endorsement/experience of that item. The EORTC QLQ-C30 can also be used to generate quality adjusted life years for economic analyses.[59 60]

Other variables

Therapeutic alliance: This is measured by the Agnew Relationship Measure—Five Item Version—Patient Rated (ARM-5[61]). This short questionnaire has been developed as a mechanism for assessing therapeutic alliance within busy clinical settings.[61] The ARM5 comprises a single 'core alliance' domain consisting of items from the ARM bond, partnership and confidence domains. The ARM5 consists of a series of statements on parallel forms rated by clients and clinicians using a seven-point Likert scale anchored 'strongly disagree', 'moderately disagree', 'slightly disagree', 'neutral', 'slightly agree', 'moderately agree' and 'strongly agree'. Clinicians and clients are asked to rate items 'thinking about today's meeting'. An overall 'core alliance' scale is derived by calculating the mean of the five items, with higher scores reflecting stronger therapeutic alliance.

Nicotine dependence: The Fagerstrom Test for Nicotine Dependence[62] is a six-item, reliable and valid self-report questionnaire designed to assess the strength of nicotine dependence. Item scores are summed to produce a total score, with higher scores indicating higher levels of nicotine dependence (0–2=very low; 3–4=low; 5=medium; 6–7=high; 8–10=very high dependence).

Expired carbon monoxide (CO) will provide biochemical verification of smoking status. Recent evidence suggests that as many as 30% of patients with HNC may misrepresent their tobacco use during treatment. The Micro 11 Smokerlyser will be used to assess breath levels of CO, with a level <10 ppm signifying abstinence from smoking.[63]

The Alcohol Use Disorders Identification Test (AUDIT[64]) is a ten item self-report measure developed by WHO to identify harmful patterns of alcohol use over the preceding 1 year (including harmful use, hazardous use and dependence). Items are summed to produce a total score, with scores over 8 indicating harmful or hazardous alcohol use, as well as possible alcohol dependence. Inspection of individual items can be used to further identify the nature of alcohol-related problems. Scores above zero on items 1–3 can signify risky or hazardous use; on items 4–6 (especially weekly or daily symptoms), scores above zero are indicative of the presence or incipience of alcohol dependence, while

endorsement of items 7–10 demonstrates that alcohol-related harm is already occurring.[65]

The AUDIT-Consumption[64] consists of the first three items of the AUDIT (frequency of use, typical consumption and frequency of six or more standard drinks), and provides an index of alcohol use. This brief questionnaire is a reliable indicator of heavy drinking and also demonstrates adequate sensitivity and specificity for detecting active alcohol abuse and dependence.[64] It will be employed to detect changes in quantity and/or type of alcohol consumed across the 18 weeks of the trial, with reference to a 2-month time frame.

Dysphagia: The research officer will conduct a secondary assessment of dysphagia as it relates to nutrition using the Australian standard of food texture. The assessor will record the participant's ability to swallow to a standard level: unmodified (regular), texture A (soft), texture B (minced moist), texture C (smooth pureed), and to drink water without coughing or choking.

Chart review

Outcome and covariate data (table 2) will also be collected by a member of the study team during chart reviews conducted during the first week of radiotherapy and at 12-week follow-up.

Chart audit

A chart audit will also be conducted on those patients who met the three key screening criteria but were not enrolled in the study. A summary of the following variables will be generated to allow for any recruitment or drop-out bias to be controlled for in analysis: standard demographics; tumour site, stage and response; proposed and delivered concurrent chemotherapy; concurrent surgery; number and frequency of dietetic consults; unplanned hospital visits, length of stay; prescribed and delivered radiotherapy dose, fractionation, treatment time and treatment interruption(s); whether a percutaneous endoscopic gastrostomy or nasogastric tube was used prophylactically, or for alimentation during treatment or post-treatment; and mortality data.

Sample size

The target sample size for this trial will be 400 (approximately 80 participants per recruitment hospital). This sample size calculation was based on a t test using the Harvard Biostatistics Massachusetts General Hospital Biostatistics Power and Sample Size Calculator, providing 80% probability that the study will detect a treatment difference at a two-sided 0.05 significance level with a minimum important difference of two units on the PG-SGA, assuming the SD is 7.

Statistical analysis

The primary outcome of nutritional status as measured by the PG-SGA will be analysed using a Generalised Linear Mixed Model to take account of the repeated measurements on subjects over time (assessment

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Table 2 Outcome and covariate data extracted during chart reviews

Week one	Twelve weeks follow-up
Tumour site	Delivered radiotherapy dose, fractionation, start date, finish date and total treatment time
Tumour stage	Treatment interruption
Concurrent chemotherapy	Unplanned hospital visits and length of stay
Concurrent surgery	Tumour response
Proposed RT dose, fractionation and treatment time	Whether PHQ-2 follow-up was documented
Prophylactic PEG/nasogastric tube feeding placement and date inserted	Number and frequency of dietetic consults
Whether PHQ-2 screening was documented	Whether PG-SGA/formal nutritional assessment was documented in the final week of treatment and the score
Whether PG-SGA/formal nutritional assessment was documented in the first week of treatment and the score	Complications with PEG/date of removal of PEG if removed
	Whether a PEG or nasogastric tube feeding was used for alimentation during treatment or post treatment and date inserted and removed
	The dates and dosage of all medications/treatments received as part of another clinical trial

PEG, Percutaneous endoscopic gastrostomy; PG-SGA, Patient Generated Subjective Global Assessment; PHQ-2, The Patient Health Questionnaire 2; RT, radiotherapy.

moment). The model will include the cluster-level variables of intervention (pre and post) and hospital. Individual-level variables in the model will be baseline nutritional status as measured by the PG-SGA, calendar time, assessment moment, as well as tumour site and tumour stage. A random effect for individual will be included in the model as well as a random effect for assessment moment, as the variation in PG-SGA is likely to be much greater at the assessment moment during the patient's treatment phase. Finally, an interaction term for intervention by assessment moment will be included in the model to allow the treatment effect to vary over time.

REGISTRATION

The trial is registered with the Australian New Zealand Clinical Trials Registry with the number ACTRN1261300 0320752.

DISCUSSION

The present study is significant in that it addresses the issue of malnutrition during radiotherapy, a major risk factor for morbidity and mortality in patients with HNC. Although mucosal cancers of the head and neck have traditionally accounted for approximately 3%[2] of all cancer diagnoses, the frequency of this diagnosis has increased exponentially in recent years. Radiotherapy plays a major role in the management of these patients, often in association with surgery or chemotherapy. This is the first study to evaluate a dietitian-delivered behaviour change intervention (EAT) based on MI and CBT to maintain or improve nutritional status among patients with HNC. The results of the proposed trial are expected to make a significant contribution to dietetic clinical practice, the training of future oncology dietitians, and ultimately, to reducing the mortality of patients with HNC.

Importantly, this study brings together existing research, clinical experience and promising pilot data collected by the research team. It is a collaboration between investigators internationally recognised in their respective fields of oncology, psychiatry, dietetics, health behaviour and systems change, working towards better outcomes for this challenging and often overlooked cancer population.

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APPENDIX A10: Paper Four – Published manuscript   A 85

BMJ Open

Eating As Treatment (EAT) study protocol: a stepped-wedge, randomised controlled trial of a health behaviour change intervention provided by dietitians to improve nutrition in patients with head and neck cancer undergoing radiotherapy

Ben Britton, Kristen McCarter, Amanda Baker, Luke Wolfenden, Chris Wratten, Judith Bauer, Alison Beck, Patrick McElduff, Sean Halpin and Gregory Carter

	Updated information and services can be found at: **http://bmjopen.bmj.com/content/5/7/e008921**

These include:

References	This article cites 53 articles, 3 of which you can access for free at: **http://bmjopen.bmj.com/content/5/7/e008921#BIBL**
Open Access	This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/
Email alerting service	Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

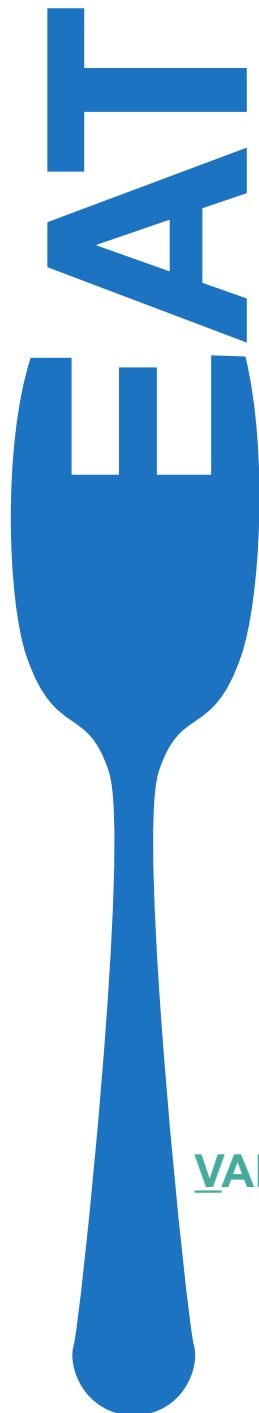| **Topic Collections**	Articles on similar topics can be found in the following collections Ear, nose and throat/otolaryngology (72) Health services research (1387) Oncology (400)

Notes

EAT

Eating as Treatment

PRINCIPLES OF BEHAVIOUR CHANGE

People are more likely to carry out a particular behaviour if:

1 they argue for the behaviour themselves

2 it is part of a concrete plan they devise themselves

3 it is recorded externally

4 they feel it is important, achievable and is being *monitored*

EAT TO LIVE

LIVING Why are you having radiotherapy?

INVITE I wonder if I can tell you something about malnutrition during treatment?

VARIANCE I'm puzzled by the difference between what you want and what you are currently doing with your nutrition

ELICIT What's the next step?

Over the past two weeks, how often have you been bothered by any of the following

EAT

Eating as Treatment

1 Little interest or pleasure in doing things

☐ Not at all (0)

☐ Several Days (1)

☐ More than half the days (2)

☐ Nearly every day (3)

2 Feeling down, depressed or hopeless

☐ Not at all (0)

☐ Several Days (1)

☐ More than half the days (2)

☐ Nearly every day (3)

Patients scoring ≥3 should be considered for referral to psychological treatment.

APPENDIX A12: Pre-site meeting checklist template

| DATE:_____ | SITE:_____ | INITIALS: _____ |

ATTENDING: _____

CHECKLIST

Executive support

Confirm executive staff are willing to:

- communicate support for the EAT intervention (i.e. introduce EAT team at training, communicate importance of the intervention, standing agenda item at staff meetings) ○

- encourage dietetic staff to attend EAT training ○

Training

- confirm the staff members attending ○
- start and finish time ○
- room booked ○

Feedback

Provide feedback on the current level of care provided by dietitians relative to guidelines (using performance feedback report) ○

Systems

Discuss current dietetic consultation scheduling procedures ○

Discuss any perceived barriers to training ○

Notes

_____

_____

_____

_____

APPENDIX A13: Pre-site meeting minutes template

DATE:_____   **SITE:_____**   **INITIALS: _____**

ATTENDING: _____

CHECKLIST

Executive support

Confirm executive staff are willing to:

- **communicate support for the EAT intervention (i.e. introduce EAT team at training, communicate importance of the intervention, standing agenda item at staff meetings)**   ◯

_____
_____
_____

- **encourage dietetic staff to attend EAT training**   ◯

_____
_____
_____

Training

- **confirm the staff members attending**   ◯

_____
_____

- **start and finish time**   ◯

_____
_____

- **room booked**   ◯

_____
_____

1

Feedback

Provide feedback on the current level of care provided by dietitians relative to guidelines (using performance feedback report) ◯

_____
_____
_____
_____
_____

Systems

Discuss current dietetic consultation scheduling procedures ◯

_____
_____
_____

Discuss any perceived barriers to training ◯

_____
_____
_____
_____
_____
_____
_____
_____
_____

Other Notes

_____
_____
_____
_____

Action Items

_____
_____
_____

2

APPENDIX A13: Pre-site meeting minutes template   A   91

APPENDIX A14: Academic detailing template

| DATE:_____ | SITE:_____ | INITIALS: _____ |

ACADEMIC DETAILING

This section will require research staff to check the implementation of intervention systems   Y=1, N=0

1. Medical prompts (stickers) have been placed on the patient records of eligible patients

2. Dietetic appointments are scheduled time adjacent to radiotherapy appointments

This section will require research staff to sit in on dietetic consultations

Research staff:

3. Identify & meet with dietetic staff
4. Ensure all dietetic staff attended EAT training
5. Ensure dietitians are aware of their site's written policy for distress screening & referral
6. Provide feedback to dietetic staff regarding patient care (see below):

INTERVENTION COMPONENTS

During shadowing, did you observe the following:	Y	N	N/A
Dietitian aims for energy intake of ≥125kj/kg/day and protein intake ≥1.2g/kg/day	○	○	○
Prophylactic tube feeding recommended for patients not tolerating adequate intake orally	○	○	○
Dietitian contact occurs weekly (during radiotherapy), at least fortnightly (for at least 6 weeks post radiotherapy) & as required (6 months post radiotherapy)	○	○	○
Dietitian monitors weight, intake & nutritional status during & post radiotherapy	○	○	○
Dietitian uses a validated nutrition assessment tool (e.g. PGSGA) to assess nutritional status	○	○	○
Dietitian uses a standardised tool to screen for distress (e.g. PHQ-2)	○	○	○
Dietitian discusses referral options for those identified as distressed (PHQ-2 score ≥3)	○	○	○

ACTION PLAN/COMMENTS

| Task: | Person responsible: | Due date: |

APPENDIX A15: Booster training questionnaire

| DATE:_____ | SITE:_____ | INITIALS:_____ | GENDER:_____ | YEAR OF BIRTH:_____ |

BOOSTER QUESTIONNAIRE

1. **For the following 6 statements, please indicate your level of agreement by choosing <u>one response</u> per item. Please do not spend too much time on each item. We are interested in your initial impressions.**

		Strongly Disagree	Disagree	Neutral	Agree	Strongly Agree
a)	I feel proficient and able to use Behaviour Change Counselling in my practice with HNC patients (now, after training):	❍	❍	❍	❍	❍
b)	My HNC patients' lack of motivation for change is a significant frustration in my work:	❍	❍	❍	❍	❍
c)	I believe that a client's own level of motivation for change is important:	❍	❍	❍	❍	❍
d)	If a HNC patient is not initially motivated, I feel able to increase his or her motivation:	❍	❍	❍	❍	❍
e)	I am interested in learning more about how to do behaviour change counselling	❍	❍	❍	❍	❍
f)	I plan to use behaviour change counselling in my future work with HNC patients:	❍	❍	❍	❍	❍

2. **For the following 10 statements, please choose *either* true or false. Please do not spend too much time on each item -we are interested in your initial impressions.**

		True	False
a)	When a patient is resistant, useful clinician responses include providing advice and arguing for change	❍	❍
b)	Reflective statements make a guess about what the patient is saying	❍	❍
c)	Reflective listening is an important way of communicating empathy and developing rapport	❍	❍
d)	Reflective statements must be accurate	❍	❍
e)	Directing a session according to what the clinician thinks the problem(s) are can compromise rapport	❍	❍
f)	Change talk is any self-expressed language that is an argument for change	❍	❍

3. **People are more likely to carry out a particular behaviour if…**

		True	False
a)	…they argue for the behaviour themselves	❍	❍
b)	…it is part of a concrete plan they devise themselves	❍	❍
c)	…it is recorded externally	❍	❍
d)	…they feel it is important, achievable and is being monitored	❍	❍

4. **Please match the following descriptions to the correct type of question (open vs. closed)**

		Open	Closed
a)	Invites the person to reflect and elaborate	❍	❍
b)	Asks for specific information	❍	❍
c)	Can help to strengthen a collaborative relationship	❍	❍
d)	Plays a key role in evoking motivation	❍	❍

5. **For each of the following pairs, please indicate which question is open and which is closed**

		Open	Closed			Open	Closed
a)	How are you feeling?	❍	❍	a)	Are you feeling well?	❍	❍
b)	Did you enjoy the sustagen?	❍	❍	b)	What was the sustagen like?	❍	❍
c)	What did you have for lunch?	❍	❍	d)	Did you have yoghurt at lunch as well?	❍	❍

PLEASE TURN OVER

EAT
Radiotherapy Nutrition Project

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

THE UNIVERSITY OF QUEENSLAND AUSTRALIA

Health NSW Hunter New England Local Health District

Australian Government National Health and Medical Research Council N H M R C

TROG CANCER RESEARCH

| DATE:_____ | SITE:_____ | INITIALS:_____ | GENDER:_____ | YEAR OF BIRTH:_____ |

These questions are about the broader support you have received over the last two months (i.e. since participating in the initial EAT workshop).

Please use the following scale (1-5) to rate aspects of the training:
  1 = "Very unhelpful," or the lowest, most negative impression
  3 = "Neither agree nor disagree" or an adequate impression
  5 = "Very helpful," or the highest, most positive impression

Regarding the support you have received from the "EAT: Radiotherapy Nutrition Project" to improve the management of head and neck cancer patients, how helpful were the following:

	Very unhelpful	Unhelpful	Neither helpful nor unhelpful	Helpful	Very helpful
STAFF VISITS					
The information provided by program staff during their visit to the clinic	○	○	○	○	○
FEEDBACK REPORTS					
The information provided in the feedback reports from the program staff	○	○	○	○	○
RESOURCES					
The prompts for key workshop principles and strategies (e.g. stickers, mugs)					
The PHQ-2 sticker	○	○	○	○	○
The medical record prompts relating to best practice clinical guidelines	○	○	○	○	○
The distress referral policy developed in collaboration with your team	○	○	○	○	○
SUPERVISION					
Meeting with the program clinical psychologist	○	○	○	○	○
Receiving feedback on audio-recordings	○	○	○	○	○
SCHEDULING					
Changing the scheduling of dietetic consultations (i.e. to occur on the same day as radiotherapy appointments)	○	○	○	○	○

COMMENTS

How could the support you have received since training be improved?

_____

_____

_____

APPENDIX A15: Booster training questionnaire   A   94

APPENDIX A16: Telephone support contact

DATE:_____	SITE:_____	INITIALS: _____

TELEPHONE SUPPORT CONTACT

Date		
Discussion with:		
Completed by:		
	Yes	No
Review actions	□	□
Review performance feedback report	□	□
Identify areas of achievement	□	□
Identify opportunities for improvement	□	□
Facilitate problem solving	□	□
Set goals	□	□
Actions		
Task	By whom	By when
1.		
2.		
3.		
4.		
5.		
Post Meeting		
Email completed template to site		
Email completed template to research team		

APPENDIX A17: Feedback report example

EAT
Radiotherapy Nutrition Project

Intervention Period Feedback Report
**June 2015 - PMCC**

Dear Sarah,

The following report provides currently available data on the delivery of the EAT intervention practices at your site during the control and intervention phases as well as the mean across all trial sites during the intervention phase.
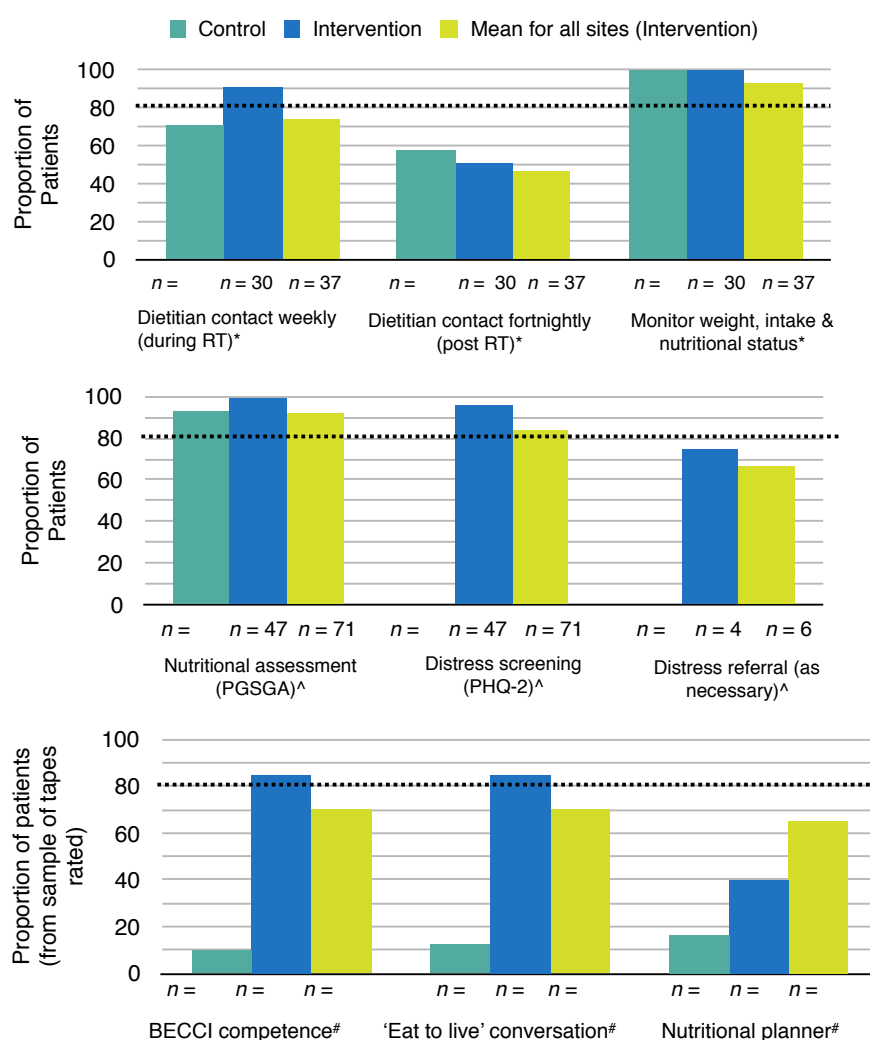
Data sources: ^Wk 1 RT Chart Review *12 Wks Post RT Chart Review # Independent, blind, ratings of a random sample of audio recordings.

Data in this report indicate that ? of the 9 practices are being delivered to 80% or more of EAT trial
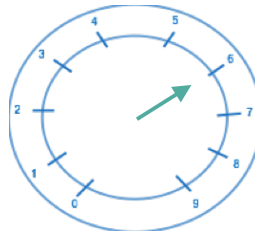
Please congratulate your team for delivering the following practices to over 80% of all EAT intervention patients:

- Dietitian contact occurs weekly during radiotherapy

- Dietitian monitors weight, intake & nutritional status during and post radiotherapy (using PGSGSA post Wk 1)

- Dietitian uses a validated nutrition assessment tool (PGSGA) to assess nutritional status (during Wk 1 of RT)

- Dietitian uses a standardised tool to screen for distress (e.g. PHQ-2)

- BECCI (meeting competence threshold of 2.57)

- 'Eat to live' conversation (to occur at a minimum of week 5 of RT)

Please discuss with your team how the following practices could be improved at your site:

- Dietitian contact occurs fortnightly for 6 weeks post radiotherapy

- Dietitian provides referral for psychosocial support to patients screened as distressed (PHQ-2 score ≥3)

- Nutritional planner (a collaborative, written nutrition plan to occur each session with specific, concrete goals that will be monitored)

[1](Behaviour Change Counselling Index; Lane, 2002) is an 11 item assessment of Behaviour Change Counselling Skills. Each item is rated on a 5 point Likert Scale from 0 to 4 ("Not at all" to "A great Extent"). The competence threshold of 2.57 is based on the post training scores achieved by Calvary Mater Dietitians during piloting.

We look forward to discussing this feedback report with you when we meet.

Feel free to contact the EAT team with any questions or feedback!

APPENDIX A18: PRISMA checklist for Paper Six

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	195
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	196
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	198
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	199
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	200
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	200
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	202
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A18
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	203

Section/topic	#	Checklist item	Reported on page #
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	203
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	203
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	203
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	205
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	205
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	205
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	206
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	206
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	211
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	212
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	211
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	217
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	219
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	220
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Appendix A19

For more information, visit: **www.prisma-statement.org**.

APPENDIX A19: PROSPERO registration for Paper Six

PROSPERO International prospective register of systematic reviews

Review title and timescale

1   Review title
Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.
Smoking cessation care amongst cancer patients: a systematic review

2   Original language title
For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3   Anticipated or actual start date
Give the date when the systematic review commenced, or is expected to commence.
27/02/2015

4   Anticipated completion date
Give the date by which the review is expected to be completed.
29/02/2016

5   Stage of review at time of this submission
Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started   ✗

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here.

Review team details

6   Named contact
The named contact acts as the guarantor for the accuracy of the information presented in the register record.
Ms McCarter

7   Named contact email
Enter the electronic mail address of the named contact.
kristen.mccarter@newcastle.edu.au

8   Named contact address
Enter the full postal address for the named contact.
CTNMH, Level 5, McCauley Centre, Mater Hospital, C/O: The Store, Platt Street, Mater Hospital, Waratah NSW 2298 Australia

9   Named contact phone number
Enter the telephone number for the named contact, including international dialing code.
6140335692

10   Organisational affiliation of the review
Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

None

Website address:

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Ms	Kristen	McCarter	School of Psychology, University of Newcastle, Australia
Dr	Ursula	Martinez	Faculty of Psychology, University of Santiago de Compostela, Spain
Professor	Amanda	Baker	School of Medicine and Public Health, University of Newcastle, Australia
Professor	Billie	Bonevski	School of Medicine and Public Health, University of Newcastle, Australia
Dr	Luke	Wolfenden	School of Medicine and Public Health, University of Newcastle, Australia
Dr	Chris	Wratten	Department of Radiation Oncology, Calvary Mater Newcastle Hospital, Waratah, Australia
Dr	Alison	Beck	School of Medicine and Public Health, University of Newcastle, Australia
Dr	Ashleigh	Guillaumier	School of Medicine and Public Health, University of Newcastle, Australia
Professor	Gregory	Carter	School of Medicine and Public Health, University of Newcastle, Australia
Dr	Ben	Britton	School of Medicine and Public Health, University of Newcastle, Australia
Dr	Sean	Halpin	School of Psychology, University of Newcastle, Australia

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
Funded by the Hunter Cancer Research Alliance

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
Examine the effectiveness of smoking cessation interventions on smoking cessation rates in adult HNC patients

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

The following electronic databases will be searched for potentially eligible studies published up to February 2016; the Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL. The MEDLINE search strategy will be adapted for other databases and will include filters used in other systematic reviews for population (head and neck cancer patients) and health behaviour (smoking cessation) will be based on Cochrane Tobacco Addiction Group standard review terms. A Google Scholar search for articles published online between 2000 to February 2016 will also be conducted. Additionally, hand searches will be performed of the reference lists of included studies. There will be no restriction on the length of the study follow-up period, or country of origin. Only studies published in English language will be included.

17   URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18   Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.
Tobacco smoking abstinence: The Cochrane Tobacco Addiction Group describes abstinence as a period of being quit, i.e. stopping the use of cigarettes or other tobacco products. It may be defined in various ways including point prevalence abstinence; prolonged abstinence; or continuous/sustained abstinence.

19   Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Participants of included studies will be adults who have been diagnosed of head and neck cancer (HNC) at any stage of treatment: the definition of HNC will include cancers involving the nasopharynx, oropharynx, oral cavity, larynx and hypopharynx. Studies will be excluded if they report on HNC patients among a more heterogeneous sample and do not report results specific to a HNC sub-group. Studies which examine the smoking cessation outcomes for carers of HNC patients will be excluded.

20   Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Any intervention that aims to improve the smoking cessation outcomes of head and neck cancer patients in which part of the intervention was conducted in a health care setting (e.g. clinics and hospitals will be considered for inclusion. Interventions could include psychosocial, behavioural (such as counselling, brief advice, web-based information and behavioural support) and/or pharmacological components (medication, NRT). Interventions targeting improvement of delivery of smoking cessation services will be included only when data for changes in smoking behaviour in sample of HNC patients were also reported. Studies that reported on population-level public health interventions (such as mass media campaigns, taxation and restrictions on tobacco advertising) will be excluded.

21   Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Any intervention with a parallel control (active, waitlisted, care as usual) group will be included.

22   Types of study to be included
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
Both randomised and non-randomised controlled trials.

23   Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.
Studies may be conducted in a variety of health settings where HNC patients receive treatment (such as clinics, hospitals, etc.). Treatment may include radiotherapy, chemotherapy, surgery or a combination of these.

24   Primary outcome(s)
Give the most important outcomes.
1. To be included in the trials needed to report a measure of smoking cessation. This could include point prevalence

APPENDIX A19: PROSPERO registration for Paper Six   A   103

or continuous measures of smoking abstinence, or current smoking status. Smoking cessation could be assessed via self-report (e.g. interviews, questionnaires and surveys) or biochemical measures (e.g. carbon monoxide (CO) or cotinine assessment).

Give information on timing and effect measures, as appropriate.

25   Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
1. While not an inclusion criteria, we extracted any measure of smoking behaviour including consumption of cigarettes per day, level of nicotine dependence, quit attempts and stage of change. Such data may be obtained from both self-report e.g. interviews, questionnaires and surveys or biochemical verification e.g. CO measures and cotinine confirmed measures.

Give information on timing and effect measures, as appropriate.

26   Data extraction (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.
Titles and abstracts retrieved by electronic searches will be exported to a reference management database (i.e. EndNote) to remove duplicates. The references will then be exported to the online software tool Covidence for screening. Two reviewers will independently screen the same 20% sample of titles and abstracts to ensure consistency. One reviewer will screen all remaining titles and abstracts. The reviewers will not be blind to the author or journal information. The full texts of manuscripts will be obtained for all potentially eligible studies for further examination. For all full-text manuscripts, the primary reason for exclusion will be recorded and documented in the excluded studies table. Discrepancies between the two review authors regarding study eligibility will be resolved by discussion and consensus and if necessary, a third reviewer. Data extraction and management: the same two reviewers will independently extract information from the included trials using a data extraction form that will be developed based on recommendations from the Cochrane Handbook for Systematic Reviews of Interventions. The data extraction form will be piloted before use. Discrepancies between reviewers regarding data extraction will be resolved by discussion and consensus and if necessary, a third reviewer. The characteristics of each study extracted, included study design, setting, country, participants, gender, age, intervention characteristics and outcomes.

27   Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Two reviewers will independently assess the risk of bias of all included studies. Studies included in the review will be assessed for methodological quality using the Effective Public Health Practice Project Quality Assessment Tool for quantitative studies. Disagreement between raters will be resolved by discussion and consensus with the involvement (if necessary) of a third reviewer.

28   Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.
It is anticipated that there will be a range of outcomes measures reported across included studies, which may make meta-analysis of the data from these trials inappropriate, in which case the findings of included studies will be presented narratively. However, if appropriate, attempts will be made to conduct meta-analysis using data from included trials.

29   Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
Where possible sub-group analysis will be conducted to determine differences by treatment modalities (i.e. radiotherapy, chemotherapy, surgery or combined), intervention type (e.g. NRT, psychological), and stage of treatment (prior, during, after).

Review general information

30   Type and method of review
Select the type of review and the review method from the drop down list.

APPENDIX A19: PROSPERO registration for Paper Six   A   104

Intervention, Systematic review

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31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Australia, Spain

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
McCarter, K., Martínez, U., Britton, B., Baker, A., Bonevski, B., Carter, G., Beck, A., Wratten, C., Guillaumier, A., Halpin. S. A., Wolfenden, L. Smoking cessation care among patients with head and neck cancer: a systematic review. BMJ Open. 2016;6:9 e012296 doi:10.1136/bmjopen-2016-012296

Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
We plan to publish this review in an open access journal.

Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)
smoking cessation

head and neck cancer

tobacco smoking

interventions

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Completed and published

01/06/2016

39   Any additional information
      Provide any further information the review team consider relevant to the registration of the review.

40   Details of final report/publication(s)
      This field should be left empty until details of the completed review are available.
      Give the full citation for the final report or publication of the systematic review.
      Give the URL where available.

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APPENDIX A20: Search strategy for Paper Six

1	RANDOMIZED-CONTROLLED-TRIAL.pt.
2	CONTROLLED-CLINICAL-TRIAL.pt.
3	PRAGMATIC-CLINICAL-TRIAL.pt.
4	CLINICAL-TRIAL.pt.
5	Qualitative research/ or qualitative
6	Random-Allocation/
7	double-blind-method/
8	single-blind-method/
9	placebos/
10	((clin$) adj5 (trial$ or placebo$ or random$).tw
11	((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).tw
12	(volunteer$ or prospective$).tw
13	exp Follow-Up-Studies/
14	exp Evaluation-Studies/ or Program-Evaluation.mp.
15	control*.tw
16	groups.tw
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
18	exp Smoking Cessation/
19	"tobacco use"/
20	"Tobacco-Use-Cessation"/
21	"Tobacco-Use-Disorder"/
22	Tobacco-Smokeless/
23	exp Tobacco-Smoke-Pollution/
24	exp Tobacco-/
25	exp Nicotine-/
26	smok*
27	Smoking/
28	cigar*
29	18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	exp HEAD/ and NECK NEOPLASMS/
31	(head or neck or upper aerodigestive tract or uadt or nasopharynx or oropharynx or oral cavity or larynx or hypopharynx) adj5 (cancer* or neoplas* or tumor* or tumour* or malignant* or car-cinom* or carcinom*)
32	30 or 31
33	17 and 29 and 32

BMJ Open | Smoking cessation care among patients with head and neck cancer: a systematic review

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ABSTRACT

Objective: To examine the effectiveness of smoking cessation interventions in improving cessation rates and smoking related behaviour in patients with head and neck cancer (HNC).

Design: A systematic review of randomised and non-randomised controlled trials.

Methods: We searched the following data sources: CENTRAL in the Cochrane Library, MEDLINE, EMBASE, PsycINFO and CINAHL up to February 2016. A search of reference lists of included studies and Google Scholar (first 200 citations published online between 2000 and February 2016) was also undertaken. The methodological quality of included studies was assessed using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP). 2 study authors independently screened and extracted data with disagreements resolved via consensus.

Results: Of the 5167 studies identified, 3 were eligible and included in the review. Trial designs of included studies were 2 randomised controlled trials and 1 non-randomised controlled trial. 2 studies received a weak methodological rating and 1 received a moderate methodological rating. The trials examine the impact of the following interventions: (1) nurse delivered cognitive–behaviour therapy (CBT) via telephone and accompanied by a workbook, combined with pharmacotherapy; (2) nurse and physician brief advice to quit and information booklets combined with pharmacotherapy; and (3) surgeon delivered enhanced advice to quit smoking augmented by booster sessions. Only the trial of the nurse delivered CBT and pharmacotherapy reported significant increases in smoking cessation rates. 1 study measured quit attempts and the other assessed consumption of cigarettes per day and readiness to change. There was no significant improvement in quit attempts or cigarettes smoked per day among patients in the intervention groups, relative to control.

Conclusions: There are very few studies evaluating the effectiveness of smoking cessation interventions that report results specific to the HNC population. The 3 trials identified reported equivocal findings. Extended CBT counselling coupled with pharmacotherapy may be effective.

Trial registration number: CRD42016016421.

Strengths and limitations of this study

- To the best of our knowledge, this is the first systematic review examining the effectiveness of smoking cessation interventions in improving cessation rates and smoking-related behaviour in patients with head and neck cancer.
- The quality of the studies included in this review were compromised by small sample sizes and reliance on self-reported outcomes of smoking cessation that were not biochemically verified in two of the three included studies.
- Varying interventions, outcomes and end points, and the limited number of studies precluded quantitative synthesis of the trial findings.

INTRODUCTION

Tobacco use is a key risk factor for head and neck cancer (HNC)[1] with more than 75% of these cancers attributable to the combination of tobacco and alcohol use.[2] Human papilloma virus is another common cause of HNC and smoking in this group while not causative, has been shown to influence prognosis significantly.[3] At least one-third of patients with HNC continue to smoke after diagnosis.[4–6] Continued smoking increases risk for other smoking-related diseases, second primary tumours,[7] disease recurrence[8] and reduced treatment efficacy, increases toxicity and side effects from radiotherapy[5 9] and negatively affects overall survival.[5] Approximately 10–12% of patients with HNC develop a new cancer in the head and neck region within 2–3 years after the first cancer diagnosis.[10]

In addition to the diverse health benefits of permanent smoking cessation, quitting can have more specific benefits for patients with a cancer diagnosis. A number of studies have reported improvements in the prognosis of patients with a cancer diagnosis following smoking cessation.[5 8 11 12] For example, quitting smoking among patients with locally

advanced HNC has been associated with a twofold increase in complete response to radiation therapy.[5] Abstinence from smoking in patients with cancer has also been associated with less pain, higher quality of life scores and better performance status.[13] Furthermore, smoking abstinence following diagnosis reduces morbidity and mortality,[5 14] particularly among those with smoking-related cancers such as HNC and those diagnosed with a curable disease.[15]

Systematic reviews of smoking cessation interventions in the general oncology population have found that high-intensity, multicomponent interventions that include a combination of pharmacological and behavioural approaches are effective in improving cessation rates.[16 17] However, no reviews of the effectiveness of smoking cessation interventions for patients with HNC exist. Patients with varying types of cancer have been found to respond differently to cessation treatment depending on the perceived relevance of patient tobacco use to the onset or recovery from cancer.[18] Further, among patients with HNC, the location of the malignancy and treatment can cause difficulty in eating, fatigue, mucositis, dry mouth and taste changes[19] that may uniquely influence patient receptivity to some pharmacotherapy interventions such as nicotine gum and require a tailored approach to cessation treatment. In addition to smoking, alcohol use is a key risk factor for HNC and a substantial proportion continue to drink alcohol, with ∼16% continuing to drink at hazardous levels after diagnosis.[4 20] Such comorbidities present further obstacles to smoking cessation in this population[21] and therefore may warrant tailored treatment. Furthermore, research in this particular cancer population has characterised patients with HNC as a particularly vulnerable group, with many living alone and having a limited social network.[22] These factors may also necessitate extra support for patients with HNC to quit smoking.

Given the importance of ceasing tobacco use among patients with HNC and the lack of guidance from previous systematic reviews regarding effective cessation treatment among this group, the primary aim of this review is to examine the effectiveness of smoking cessation interventions on smoking cessation rates in adult patients with HNC.

METHODS

This systematic review was performed in accordance with a predetermined protocol and is reported to be consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[23] The review was prospectively registered with PROSPERO (CRD42016016421).

Eligibility criteria
Study characteristics
Types of studies
Studies with the following study designs were considered for inclusion:
- Randomised controlled trials, including cluster randomised controlled trials;

- Staggered enrolment trials or stepped-wedged trials;
- Quasi-randomised trials;
- Quasi-experimental trials with comparison/control groups, including non-randomised pre–post (before–after) trials with one or more intervention and control groups, time-series/interrupted time-series trials (including multiple baseline trials) with independent control groups, preference trials and regression discontinuity trials;
- Natural experiment studies that have a comparison group.

Trials without parallel comparison or control groups were excluded. There was no restriction based on length of follow-up or the year of publication. Studies were limited to those published in English in peer-reviewed scientific journals. Comparison groups for included trials could include no intervention controls, 'usual' practice or alternative interventions.

Participants
Participants of included studies were adults diagnosed with HNC (including cancers of the nasopharynx, oropharynx, oral cavity, larynx and hypopharynx) and current smokers or those who had recently quit, due to the potential for relapse. There were no restrictions on type (eg, radiotherapy, surgery, chemotherapy) or stage (eg, pre, during, post) of treatment. Studies that examined a heterogeneous group of patients with cancer but did not report results specific to an HNC subgroup were excluded. Studies that examined smoking cessation for carers of patients with HNC were also excluded.

Types of interventions
Interventions that aimed to improve the smoking cessation outcomes of patients with HNC in whom part of the intervention was conducted in a healthcare setting (eg, clinics and hospitals) were included. Interventions could include psychosocial and behavioural (such as counselling, brief advice, referral, web-based information and behavioural support) and/or pharmacological components (medication, nicotine replacement therapy (NRT)). Interventions targeting improvement of delivery of smoking cessation services were included only when data for changes in smoking outcomes of patients with HNC were also reported. Studies that reported on population-level public health interventions (such as mass media campaigns, taxation and restrictions on tobacco advertising) were excluded.

Outcomes
Primary outcome:
- To be included, trials needed to report a measure of smoking cessation. This could include point prevalence or continuous abstinence, or current smoking status. Smoking cessation could be assessed via self-report (eg, interviews, questionnaires and surveys) or biochemical measures (eg, carbon monoxide or cotinine assessment).

Secondary outcomes:

▶ While not an inclusion criterion, we extracted any additional measures of smoking behaviour reported in trials as a study outcome including consumption of cigarettes per day, level of nicotine dependence, quit attempts and stage of change. Such data may be obtained via self-report (eg, interviews, questionnaires and surveys) or other methods.

Information sources
Electronic databases
The following electronic databases were searched for potentially eligible studies published up to February 2016: the Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE (from 1946), EMBASE (from 1947), PsycINFO (from 1806) and CINAHL (from 1937). The MEDLINE search strategy (see online supplementary appendix A) was adapted for other databases and included filters used in other systematic reviews for population (patients with HNC) and was based on the Cochrane Tobacco Addiction Group standard review terms for health behaviour (smoking cessation).

Other sources
Studies were also obtained from the following sources:
▶ Reference lists of included studies;
▶ A search of Google Scholar (published online between 2000 and February 2016—the first 200 citations were examined).

Study selection
The titles and abstracts retrieved by electronic searches were exported to reference management software (Endnote V.X6) to remove duplicates. References were exported to the online software tool Covidence for screening. One reviewer (UM) performed title and abstract screening. Two reviewers (KM and UM) then independently performed full-text screening, data extraction and quality assessment. Reasons for exclusion of full texts were recorded and documented in figure 1. Any discrepancies were resolved by discussion between the reviewers.

Data extraction
Two review authors (KM and UM) independently extracted data from the included trials using a prepiloted data extraction form that was developed based on recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.[24] Discrepancies between reviewers regarding data extraction were resolved by discussion and consensus. The characteristics of each study were extracted, including study design, setting, country, participants, gender, age, intervention characteristics and outcomes.

Assessment of methodological quality
Studies included in the review were assessed for methodological quality using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP) for quantitative studies.[25] This tool covers any quantitative study design, includes components of intervention integrity and was judged suitable for use in systematic reviews of effectiveness.[24 26] Two review authors (KM and UM) independently assessed study quality and discrepancies were resolved through discussion. The EPHPP assesses six methodological dimensions: selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts. These domains are rated on a three-point scale (strong, moderate, weak) according to predefined criteria and procedures recommended for tool use, and then given an overall global rating. Those with no weak ratings were given an overall rating of strong, whereas those with one weak rating were given an overall rating of moderate and those with two or more weak ratings across the six domains were given an overall weak rating. Two additional methodological dimensions provided by the tool are intervention integrity and analyses and these were also completed by the reviewers.

Data analysis
Summary measures
We reported all statistically significant and non-significant outcomes. Owing to the clinical and methodological heterogeneity and the small number of studies included in the review, meta-analysis was not performed and the study findings were synthesised narratively.

RESULTS
Search results
Abstracts of 5167 citations were screened and the full text of 29 manuscripts was sought for further assessment against the review inclusion criteria (figure 1). Of these, four publications describing three trials were included in the review.[4 15 27 28]

Study characteristics
A description of the trial characteristics of included studies is provided in table 1. Included studies were published between 1991 and 2006. Two randomised controlled trials (RCTs)[4 15 28] and one non-RCT[27] were identified. All trials compared interventions with a usual care no intervention control. All three studies were conducted in the USA. The interventions employed in Gosselin et al[27] and Gritz et al[15 28] targeted smoking cessation alone, whereas the study by Duffy et al[4] targeted multiple risk behaviours of smoking, alcohol use and depression.

The follow-up periods varied from 1 to 12 months postintervention. All studies were multicentre and participants were recruited from clinics that provided care to patients with HNC. Interventions were delivered at the
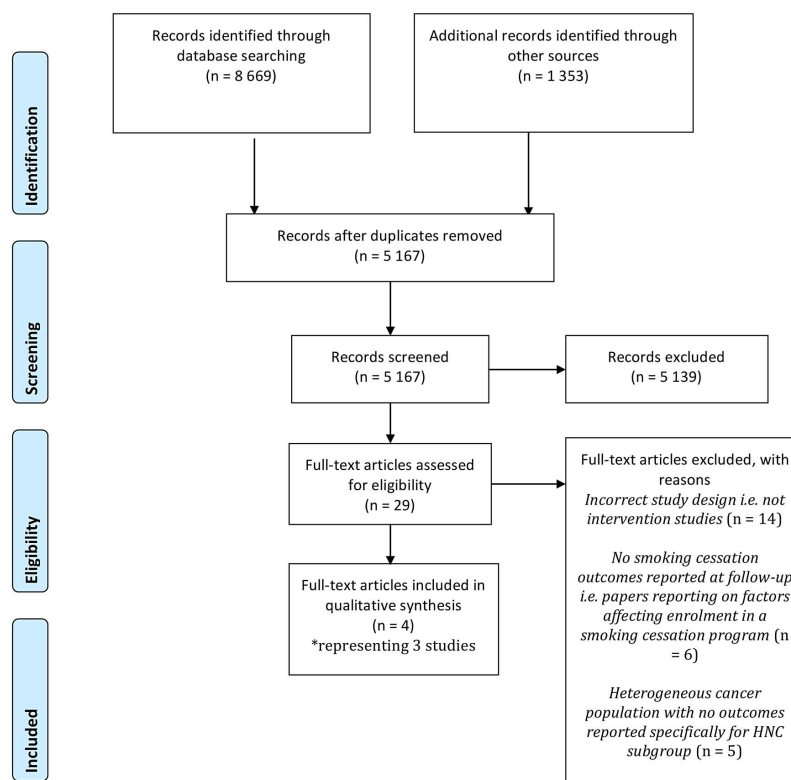
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diagnosis/treatment stage of the cancer care continuum, including pretreatment to post-treatment. Two of the three studies reported the location of the HNC in participants.[4 15] Only one study[15] reported the type of cancer treatment patients received (radiation or surgery). Smoking cessation interventions were delivered by healthcare providers and were either non-pharmacological alone (cognitive–behaviour therapy (CBT), self-help material, telephone counselling) or combined with a pharmacological component (NRT, varenicline or bupropion; table 2). In all studies, the control group received usual care, ranging from information on the risks of continued smoking and the benefits of cessation, to handouts for resources, to referral for smoking cessation treatment.

Methodological quality assessment

Individual ratings for each study against the six methodological criteria and the assigned global rating are reported in table 3. Overall, two studies received a methodological quality rating of weak[4 27] and one study received a rating of moderate.[15 28] Unrepresentative samples and non-reporting of blinding of participants and outcome assessors were key issues. Two studies relied solely on self-reported smoking status[4 27] and one used urinary cotinine to confirm smoking status.[15 28]

The two additional methodological dimensions provided by the EPHPP tool, intervention integrity and analyses, were also completed. All three studies measured the percentage of participants who received the intervention as intended and were scored in the 80–100% category on this dimension. With regard to consistency of the interventions, Duffy et al[4] did not describe whether the intervention was provided to all participants in the same way. Gosselin et al[27] reported that a proportion of the participants in the intervention condition had multiple clinic visits compared with the other intervention participants who had one visit. Gritz et al[15 28] used exit checklists to ensure that their intervention was delivered consistently, with each component delivered to

Table 1 Trial characteristics

Author year (Ref)	Study type	Study dates	Single-centre or multicentre	Setting	Country	Aim	Inclusion criteria	Number of patients at start of intervention	Mean age (years)	Gender M (%)	Tumour site/tumour stage	Cancer treatment type/stage of treatment
Duffy *et al* 2006[4]	RCT	2000–2003	Multi (4 hospitals)	ENT clinic, telephone. 4 hospitals including the University of Michigan Medical Center and 3 VA hospitals in Ann Arbor, MI, Gainesville, FL, and Dallas, TX	USA	To develop and test a tailored intervention for patients with HNC that included CBT, nicotine replacement therapy, and selective serotonin reuptake inhibitor management for smoking, alcohol use and depression	Patients with HNC from the time of diagnosis and thereafter who: (1) screened positive for 1 or more of the 3 health problems of smoking, alcohol and depression; (2) were not pregnant; and, (3) were >18 years of age	184 (91 UC; 93 I)	57 years (9.9 SD)	84		Larynx 33%, oropharynx/ hypopharynx 30%, oral cavity/other 37% stage 0, I or II 39%, stage III, IV 61%	NR/both new and post-treatment
Gosselin *et al* 2011[27]	Quasi-experimental design	UC group patients recruited between: May 2007 and June 2007; EC group patients recruited between: July 2007 and August 2007	Multi (2 clinics)	Dental/ maxillofacial or head and neck clinic, telephone. Roswell Park Cancer Institute (Buffalo, NY)	USA	To evaluate the effectiveness of a brief staff training programme on improving the delivery of tobacco cessation services to patients with head and neck cancers	Current tobacco users (ie, cigarettes, cigar, pipe, smokeless/chewing tobacco or some other type of tobacco)	179 (98 UC; 81 EC)	55.8% in 53–60 years quartile	86.8	NR/NR	NR/new and established patients
Gritz *et al* (1993, 1991)[15 28]	RCT	NR	Multi (10 clinics)	Clinic. Sites included 3 university hospitals (including both the head and neck and the maxillofacial clinics at UCLA, the main site), 3 Veterans Administration medical centres, 2 county hospitals, a health maintenance organisation hospital, and an armed services hospital (CA)	USA	Assess the efficacy of a provider-delivered smoking cessation intervention for patients with head and neck cancer	Adult (over 18 years of age) patients with newly diagnosed squamous cell carcinomas of the head and neck who met the following criteria: (1) life expectancy of more than 1 year; (2) tobacco use within the past year; (3) absence of gross psychopathology; (4) medical follow-up by local providers; (5) English speaking and reading; and (6) agreement to undergo treatment.	186 (92 UC; 94 I)	58.5 years	73.7	Oral Tumours 60.9% (buccal cavity 54.9%; n=101 and pharynx 6.0%; n=11) and laryngeal 39.1% (n=72)/ stage I and II 31.1% (n=57), stage III 44.3% (n=81) and stage IV 24.6% (n=45)	Radiation only 28.5% (n=53), total laryngectomies 24.7% (n=46), surgeries other than total laryngectomy which may have been followed by radiation 46.8% (n=87)/ spanned pretreatment to post-treatment

CA, California; CBT, cognitive–behaviour therapy; EC, enhanced cessation; ENT, ear, nose and throat; FL, Florida; HNC, head and neck cancer; I, intervention; MI, Michigan; NR, not reported; NY, New York; RCT, randomised controlled trial; TX, Texas; UC, usual care; UCLA, The University of California, Los Angeles; VA, Veterans Affairs.

Table 2 Intervention description

	Description		
	Intervention		
	Non-pharmacological	Pharmacological	Control
Duffy *et al*[4]	Nurse administered. CBT workbook, CBT telephone counselling (9–11 sessions)	Those who smoked were offered nicotine replacement therapy and/or bupropion, and those with depression were offered antidepressants.	Enhanced usual care; referred as needed for smoking cessation, and/or alcohol treatment, and/or psychiatric evaluation. Handout for local, state and national resources tailored to each study site
Gosselin *et al*[27]	Nurse and physician administered. Inquired about tobacco use, advised patients to quit, and offered assistance to tobacco users interested in quitting. Information packets were made available for staff to give to patients who reported current tobacco use. Attempts to contact all patients by phone within 10 days of visiting the clinic were assigned to a designated researcher who was trained in the delivery of support and cessation counselling components at the New York State Smokers Quitline. They were also contacted 1 month after clinic visit.	Prescription of stop smoking medication for eligible patients; varenicline and bupropion	Usual care; standard tobacco cessation practices administered by health providers with regard to asking patients about their tobacco use status or providing assistance to quit smoking at Roswell Park Cancer Institute
Gritz *et al*[15, 28]	Delivered by head and neck surgeons or maxillofacial prosthodontists. Enhanced initial advice (supplemented the usual care advice with a discussion of the participant's receptivity to quitting; a statement of confidence in the participant's ability to stop; presentation of 3 self-help booklets; a discussion of tobacco withdrawal; a discussion to determine a target quit date, including joint signature of the quit-smoking contract; and an affirmation of continuing provider support during follow-up care) session augmented by 6 booster sessions.		Usual care; standardised advice consisting of information on the risks of continued smoking and the benefits of cessation for patients with head and neck cancer. No guidelines regarding additional advice sessions; providers were free to follow their usual practice regarding discussing patient smoking practices.

CBT, cognitive–behaviour therapy.

6

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Table 3 Ratings of methodological quality: strong, moderate and weak

	Selection bias	Study design	Confounders	Blinding	Data collection	Withdrawals	Global rating
1. Duffy et al[4]	Weak	Strong	Strong	Moderate	Weak	Strong	Weak
2. Gosselin et al[27]	Moderate	Strong	Weak	Moderate	Weak	Moderate	Weak
3. Gritz et al[15 28]	Moderate	Strong	Strong	Weak	Strong	Moderate	Moderate

almost all participants in the intervention condition. However, since the health providers in this study gave advice in the control and intervention conditions, there was evidence that some contamination may have occurred. Both Duffy et al[4] and Gosselin et al[27] used intent-to-treat analyses as appropriate.

Effects of intervention

Tables 3 and 4 describe the intervention characteristics and results of the included studies, respectively. All three included studies reported smoking cessation outcomes.

Duffy et al[4] conducted an RCT to test a tailored smoking, alcohol and depression intervention in 184 patients with HNC recruited from four hospitals in the USA and conducted in ear, nose and throat clinics. The CBT intervention addressed smoking, alcohol and depression and used a workbook for patients and telephone counselling delivered by nurses in combination with NRT and/or bupropion (and antidepressants for depression) to target comorbid conditions (smoking, alcohol use and depression). The control group received enhanced usual care. The primary smoking cessation outcome in this study was self-reported smoking status (patients asked if they were currently smoking) measured at 6 months postintervention. The authors found that (for the 136 patients with HNC who smoked in the past 6 months at baseline) at 6-month follow-up, the intervention group reported significantly higher quit rates than those in the usual care group (47% vs 31%, p<0.05). The authors did not measure any additional outcomes of smoking-related behaviour.

Gosselin et al[27] conducted a study with a quasi-experimental design in 179 patients with HNC recruited from a dental/maxillofacial clinic and a head and neck clinic in the USA. The study compared the smoking behaviours of those who visited the clinic during a usual care phase (standard tobacco cessation practices) with those who visited the clinic during the intervention phase. The intervention phase employed nurse and physician brief advice to quit, information booklets and pharmacotherapy (varenicline and bupropion) during the clinic visit as well as a follow-up phone call within 10 days after the clinic visit to provide cessation counselling support. The primary smoking cessation outcome was self-reported smoking status (patients asked if they were currently smoking) at 1-month postintervention. The intervention was not effective in significantly increasing quit rates at 1-month follow-up with

intention-to-treat (assumption that those lost to follow-up had all returned to smoking) quit rates 8% for the control group compared with 9% in the intervention group.

Gosselin et al[27] also measured self-reported quit attempts (those who reported that they were currently smoking were subsequently asked whether or not they had made any attempt to stop smoking during the past month) at 1-month follow-up postintervention. No significant difference was found between intervention and control groups. No other smoking behaviours were reported.

Gritz et al[15 28] conducted an RCT to assess the efficacy of a provider delivered smoking cessation intervention compared with usual care advice in 186 patients with HNC recruited from 10 hospital or medical centre clinics in the USA. The intervention group received surgeon delivered enhanced advice (see table 3) to quit smoking augmented by six monthly booster sessions compared with a usual care control group. The authors reported three smoking cessation outcome measures: (1) ever quit (abstinent for 48 consecutive hours or longer at any time during the 12-month follow-up postintervention period after receiving initial smoking cessation advice); (2) point prevalence abstinence (abstinent for 48 hours or longer at the time of the 1-month, 6-month or 12-month follow-up interviews); and (3) continuous abstinence (abstinent at the 1-month, 6-month and 12-month interviews with no smoking at all after cessation). Cotinine validation of self-reported abstinence was also conducted at each follow-up point. No significant differences were found for any of the smoking cessation outcomes.

Gritz et al[15 28] also measured change in consumption of cigarettes per day from baseline at 12-month follow-up. Participants who were smoking at 12-month follow-up (n=30) had significantly reduced their consumption during the study, from 25.4 cigarettes/day at baseline to 12.5 at 12 months (p=0.0001). However, relative to the control group, such reductions were not significant. The study also reported readiness to stop using tobacco at baseline by questionnaire and classified according to the stage of change theory into four stages: precontemplator (not currently thinking about stopping smoking), contemplator (thinking of stopping within 1 year), action (quit within the past) and maintenance (quit for 6–12 months). The authors reported a relationship between cessation behaviours (at 12-month

Table 4 Tobacco smoking cessation characteristics

Author year (Ref)	Number of patients at start of intervention	Current smokers at baseline; outcome measure	Usual care (number of patients) at follow-up	Intervention (number of patients) at follow-up	Primary outcome		Secondary outcomes	
					Description and follow-up interval	Results	Description and follow-up interval	Results
Duffy et al 2006[4]	184 (91 UC; 93 I)	148 (68 UC; 80 I); self-report (smoked in the past 6 months)	62/68 (91 including those not 'smokers' at baseline)	74/80 (93 including those not 'smokers' at baseline)	Self-reported smoking status (patients asked if they were currently smoking); 6 months postintervention	χ^2 tests of association using ITT analysis: significant difference in smoking cessation with 47% (35/74) quitting in the intervention group vs 31% (19/62) quitting in the usual care group (p<0.05)	Subgroup analyses: self-reported smoking cessation rates; 6 months postintervention	Smoking cessation rates for only those smokers with comorbid depression and/or alcohol (omitting those who smoked only; n=101); the quit rates remained higher in the intervention group (48%) compared with the usual care group (26%; p<0.05). All patients who smoked in the past 6 months were included as smokers and, as expected, those who smoked more recently were significantly less likely to quit in the enhanced usual care and intervention groups (p<0.001).
Gosselin et al 2011[27]	179 (98 UC; 81 EC)	179 (98 UC; 81 EC); self-report current tobacco use (105 cigarettes, 2 cigars, 1 pipe, 1 chew)	60/98	52/81	Self-reported smoking status (patients asked if they were currently smoking); 1-month postintervention	χ^2 statistic was used to evaluate differences between the EC and UC groups on smoking behaviour reported. Non-ITT quit rates (assumption that those lost to follow-up were missing at random): EC, 14% vs UC, 13% at 1 month (NS). ITT quit rates (assumption that those lost to follow-up had all returned to smoking): EC, 9% vs UC, 8% at 1 month (NS)	Self-reported quit attempt (those who reported that they were currently smoking were subsequently asked whether or not they had made any attempt to stop smoking during the past month); 1-month follow-up postintervention	χ^2 statistic was used to evaluate differences between the EC and UC groups on smoking behaviour reported. Quit attempts at 1-month: I, 56% vs UC, 55% (NS)
Gritz et al (1993, 1991)[15 28]	186 (94 UC; 92 I)	164; self-report (currently smoking or stopped smoking	56/92	58/94	Smoking cessation; ever quit (abstinent for 48 consecutive hours or longer at any time during the 12-month follow-up	No significant differences between intervention and control at any follow-up on any of the 3	Consumption of cigarettes per day. Stage of change; 12-month follow-up (for participants who were current	Participants who were smoking at 12 month follow-up (n=30) had significantly reduced their consumption during the

Continued

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Table 4 Continued

Author year (Ref)	Number of patients at start of intervention	Current smokers at baseline; outcome measure	Usual care (number of patients) at follow-up	Intervention (number of patients) at follow-up	Primary outcome		Secondary outcomes	
					Description and follow-up interval	Results	Description and follow-up interval	Results
		<1 month prior to the baseline interview			postintervention period after receiving initial smoking cessation advice) Point prevalence abstinence (abstinent for 48 hours or longer at the time of the follow-up interview); 1-month, 6-month or 12-month continuous abstinence (abstinent at the interview with no smoking at all after cessation); 1 month, 6 months and 12 months Cotinine validation of self-reported abstinence	smoking cessation outcomes. I, 80% vs 79.8% at 1 month (NS). I, 84.3% vs UC, 82.6% at 6 months (NS). I, 91.4% vs UC, 89.3% at 12 months (NS). I, 69.4% vs UC, 76.2% at 1 month (NS). I, 71.4% vs UC, 73.9% at 6 months (NS). I, 69% vs UC, 78.6% at 12 months (NS). I, 69.4% vs UC, 75% at 1 month (NS). I, 64.3% vs UC, 71% at 6 months (NS). I, 63.8% vs UC 76.8% at 12 months (NS). Urine samples were collected from 83.8% (258 of 308) of participants who reported abstinence. Cotinine validations rates were 85.6% at 1 month, 91.3% at 6 months, 89.6% at 12 months	smokers at baseline n=96). Predictors of 12-month continuous abstinence (applied to the 96 baseline smokers who completed the trial)	study, from 25.4 cigarettes/day (SD=12.8) at baseline to 12.5 (SD=8.1) at 12 months (t=7.67; p=0.0001). No significant difference between I and UC participants. χ^2 of the discrepancy between larger number of precontemplators in I group and larger number of participants in the action stage of change in the UC group (p=0.017) Stepwise logistic regression; action stage of change (p=0.0004) entered the model as significant.

C, control; EC, enhanced care; I, intervention; ITT, intention to treat; NS, not significant; UC, usual care.

follow-up) and baseline readiness to change in the 96 patients who were classified as baseline smokers in their study (p=0.002). Rates of continuous abstinence at 12-month follow-up were lowest for those in the precontemplation stage and highest for those in the action stage of change at baseline. No other smoking behaviours were reported as outcomes in the trial.

DISCUSSION

The objective of the present review was to examine the effectiveness of smoking cessation interventions to improve cessation rates in patients with HNC. Despite including both randomised and non-randomised trials, the review identified only three eligible studies. Of these, only one reported significant improvements in cessation rates at follow-up. These findings highlight the lack of robust smoking cessation intervention research conducted among patients with HNC, a group where ceasing tobacco use is particularly important.

All three studies employed interventions delivered by a health provider involved in the care of patients with HNC. Health professionals in the oncology setting are well positioned to deliver smoking cessation interventions and indeed numerous best practice guidelines recommend that those involved in the care of patients with cancer assess smoking status and offer support to quit.[29] Interestingly, however, trials testing (1) nurse and physician brief advice to quit and information booklets combined with pharmacotherapy; and (2) surgeon delivered enhanced advice to quit smoking augmented by booster sessions were ineffective. Such findings are consistent with previous trials and reviews of physician-administered and nurse-administered interventions for patients with cancer who have found that relatively brief interventions are ineffective.[29–31] Patients with smoking-related cancers generally have high levels of nicotine dependence, which affects quitting success.[29 32] More intensive smoking cessation interventions may be required to improve quit rates in this population.

Indeed, the only study in this review to find statistically significant differences between intervention and control groups on the primary cessation outcome was Duffy et al.[4] The intervention used in this study was high intensity and multicomponent, with up to 11 telephone counselling sessions that targeted multiple risk behaviours with CBT and pharmacotherapy. This finding suggests that low-intensity or single intervention components that are sufficient for other patient groups may not be adequate to achieve cessation among patients with HNC characterised by long histories of heavy smoking and high nicotine dependence.[33 34] Smoking cessation research in hospitalised patients has found that intensive smoking cessation interventions combining behavioural interventions with cessation medication maximise the likelihood of a positive long-term cessation outcome.[35–37] Further trials of smoking cessation interventions in patients with HNC are needed to test this hypothesis,

specifically randomised comparisons of long-term biochemically verified smoking cessation outcomes between patients receiving high-intensity, combined behavioural intervention and pharmacotherapy with low-intensity single component interventions.

Our finding also fits with the results of previous research that integrated treatment is effective for coexisting problems.[16 38 39] The health behaviours of patients with HNC, particularly smoking and drinking, are highly inter-related. A large proportion of patients with HNC who smoke also have a history of regularly consuming alcohol.[21] Difficulties with nutrition due to the malignancy and treatment have been associated with smoking and problem drinking in HNC.[40] Given the co-occurrence of these behaviours in addition to the high rate of depression found in this group, addressing the interaction between smoking, drinking and depression in patients with HNC may be more beneficial for smoking cessation outcomes than targeted smoking treatment that ignores these other factors. The authors would cautiously suggest that multicomponent and integrated treatment be clinically recommended where available, while the evidence base is improved.

An important limitation of the review was the quality of studies included. Two studies received a methodological rating of weak and one received a rating of moderate. Although two of the three studies used a RCT design, the sample sizes were relatively small with the number of participants below 200 for all three studies. Only Gritz et al[15 28] confirmed smoking cessation status with biochemical verification. Biochemical verification of smoking status is recommended in studies of smoking cessation in medical populations with smoking related diseases.[41] Research suggests that biochemical verification of current smoking status among patients with cancer can be as much as 20% higher than self-report.[42 43] As such, the cessation outcomes reported in the included trials may represent an overestimate. Additionally, varying interventions, outcomes and end points, as well as the limited number of studies, precluded quantitative synthesis of the trial findings. While the review methods were based on the Cochrane handbook, the search was restricted to English language peer-reviewed publications. In doing so, the review may not have captured all relevant studies in the field.

CONCLUSIONS

There are very few studies evaluating the effectiveness of smoking cessation interventions that report results specific to the HNC population. The results of this review indicate that a multicomponent approach may benefit patients with HNC who continue to smoke after diagnosis. However, this finding is based on one study, and therefore the current state of evidence does not allow for a recommendation of any specific form of smoking cessation treatment, in particular for this cancer group. There is much scope for developing the evidence base

in this area. Given the significance of tobacco smoking as a key risk factor for HNC and its impact on treatment outcomes and further disease, it is imperative that further studies with strong methodological quality and standardised outcome measures are conducted in this population to guide development of smoking cessation programmes.

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Smoking cessation care among patients with head and neck cancer: a systematic review

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