Randomised Controlled Trials of Interventions to Prevent Oral Mucositis in Patients Undergoing Treatment for Cancer

A Thesis submitted to the University of Manchester for the Degree of Doctor of Philosophy in the Faculty of Medical and Human Sciences

2010

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Abstract

Introduction

Oral mucositis is an inflammatory and frequently ulcerative side effect of cancer therapy, which has been identified by patients as the most debilitating side effect of their treatment. Mucositis is a dose limiting toxicity which exerts a substantial clinical and economic impact and negatively affects patient quality of life. The patient experience of mucositis is under-reported in the literature. To date, no interventions have been identified that have proven successful in the prevention of mucositis for patients receiving all types of therapy. Vitamin E has shown conflicting results in clinical trials. This thesis combines appraisal of the literature and empirical research, and uses lessons learned from previous studies together with the results of a feasibility study to identify a best practice model for future trials.

Methods

The Cochrane risk of bias (ROB) instrument was used to assess the ROB in the studies included in the Cochrane prevention review. A sensitivity analysis was conducted after studies assessed at unclear or high risk of overall bias were excluded. A systematic review of assessment instruments was conducted which identified 50 instruments. Consideration of the appropriateness of these instruments for the use in a clinical trial for the prevention of mucositis was based on the practicality, comparability, and reproducibility, and the impact of these instruments on patients. Three of these instruments were chosen for use in a clinical trial of adults undergoing stem cell transplant. Finally, a feasibility study was designed, developed and conducted which investigated vitamin E for the prevention of mucositis in patients undergoing conditioning for bone marrow transplantation. Through lessons learned from previous studies, consultations with medical professional, the MHRA, ethics committee and suppliers, a protocol was developed for a double blind RCT. The process of gaining MHRA and ethical approval, and the repackaging of intervention and placebo products to meet MA-IMP requirements are described.

Results

130 articles were assessed for risk of bias. Only ten studies were assessed as being at low overall risk of bias. Blinding of outcome assessors and adequate allocation concealment were identified to be important considerations in the planning of future studies. Although only nine patients were recruited into the feasibility study, a number of issues affecting the design and conduct of future trials were identified. Recruitment in particular was identified to be problematic. Strategies for overcoming this problem in future trials were discussed. The methods of blinding and allocation concealment employed were found to be feasible for use in future trials. Expected adverse events patients undergoing stem cell transplantation were also reported.

Conclusion

Further studies are required to investigate interventions for the prevention of mucositis. It is of upmost importance that these trials are rigorous in both their methodology and subsequent reporting in order to elicit the maximum benefit for patients taking part in clinical trials, and future patients undergoing therapy for cancer.

Declaration

No portion of the work referred to in the thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

Copyright

Published work

Gibson F, Auld E M, Bryan G, Coulson S, Craig J V, Glenny A M. 2010. A systematic review of oral assessment instruments: what can we recommend to practitioners in children's and young people's cancer care? *Cancer Nursing,* 33**,** E1-E19.

Molassiotis A, Bryan G, Caress A, Bailey C, Smith J. 2010. Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: A systematic review of the literature. *Respiratory Medicine,* 104 (7), 934-944.

*Glenny AM, Gibson F, Auld E, Coulson S, Clarkson JE, Craig JV, Eden OB, Khalid T, Worthington HV, & Pizer, b. 2010. The development of evidence-based guidelines on mouth care for children, teenagers and young adults treated for cancer. *European Journal of Cancer,* 46**,** 1399-412.

*Craig JV, Gibson F, & Glenny AM, 2010. Audit to monitor the uptake of national mouth care guidelines for children and young people being treated for cancer. *Supportive Care in Cancer*. **In press**

Worthington H V, Clarkson JE, Bryan G, McCabe M, Furness S, Glenny AM, Littlewood A, Khalid T, Meyer S. Interventions for preventing oral mucositis for patients with cancer receiving treatment. Cochrane Database of Systematic Reviews, 2010. **In press**

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List of Abbreviations

5-FU	5-Fluorouracil
ADA	American Dietetic Association
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
AOR	Adjusted odds ratio
ALL	Acute lymphoblastic leukaemia
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BEAM	Bischloroethyl nitrosourea etoposide ara-c melphalan
BMI	Body Mass Index
BMT	Bone marrow transplantation
BSA	Body surface area
CALGB	Cancer and Leukaemia Group B
CCLG	Children's Cancer and Leukaemia Group
CCU	Critical care unit
CD	Cyclophosphamide, Dexamethasone
CHART	Continuous Hyperfractionated Accelerated Radiotherapy Trial
CI	Confidence interval
CLL	Chronic lymphocytic leukaemia
CM	Centimetre
CML	Chronic myeloid leukaemia
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase 2
CRP	C-reactive protein
CSOM	Cumulative score of oral mucositis
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Cyclophosphamide, Thalidomide and Dexamethasone
CVAD	Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone
CZDEX	Cyclophosphamide, Idarubicin and Dexamethasone
Df	Degrees of freedom
DIM	Daily Index of Mucositis
DNA	Deoxyribonucleic acid
DVT	Deep vein thrombosis
EBMT	European Group for Blood and Marrow Transplantation
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
F	Female
G-CSF	Granulocyte colony-stimulating factor
GF	Growth factor
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal

GM-CSF	Granulocyte macrophage colony-stimulating factor
Gy	Gray
HLA	Human leukocyte antigen
HSV	Herpes simplex virus
IBS	Irritable Bowel Syndrome
IGA	Immunoglobulin A
IGG	Immunoglobulin G
IL-6	Interleukin-6
IL-β	Interluekin-1 Beta
IMPD	Investigational Medicinal Product Dossier
ITT	Intention to treat (analysis)
IV	Intravenous
KG	Kilogram
LDH	Lactate dehydrogenase
LREC	Local Research Ethics Committee
M	Male
MA-IMP	Marketing Authorisation Investigational Medicinal Product
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MEL	Melphalan
MHRA	Medical and Healthcare products Regulatory Agency
MM	Multiple myeloma
MMP3	Matrix metalloproteinase 3
MRC	Medical Research Council
N	Number
NF-kβ	Nuclear factor-kβ
NHL	Non Hodgkin's lymphoma
NHS	National Health Service
NIH CTC	National Institute of Health Common Toxicity Criteria
OAG	Oral Assessment Guide
OM	Oral Mucositis
OMAS	Oral Mucositis Assessment Scale
OMDQ	Oral Mucositis Daily Questionnaire
OMI	Oral Mucositis Index
OR	Odds ratio
PAD	Bortezomib, Doxorubicin and Dexamethasone
PG-SGA	Patient Generated Subjective Global Assessment
PROMS	Patient-Reported Oral Mucositis Scale
QP	Qualified Person
RCT	Randomised controlled trial
REC	Research ethics committee
RNA	Ribonucleic acid
ROB	Risk of Bias
ROS	Reactive oxygen species
RR	Risk Ratio
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SAE	Serious adverse event

SAR	Serious adverse reaction
SD	Standard Deviation
SOD	Superoxide dismutase
SPSS	Statistical package for the social sciences
SUSAR	Suspected unexpected serious adverse reaction
TBI	Total body irradiation
TNF	Tumour necrosis factor
USA	United States of America
VAD	Vincristine, Adriamycin and Dexamethasone
VAS	Visual analogue scale
VEL DEX	Velcade, Dexamethasone
WBC	White blood cell
WCCNR	Western Consortium for Cancer Nursing Research
WHO	World Health Organisation

Acknowledgements

This PhD could not have been completed without the participation of the nine individuals who consented to take part in the trial at a very difficult time in their lives. I thank them and their families for their patience, their altruism, their good humour and their unstinting support during a terribly debilitating and painful medical procedure.

I must also thank all the staff on the Haematology Ward for their helpful advice, trust and support, and allowing a novice researcher access to their patients.

I am exceedingly grateful to my supervisors, Professor Alex Molassiotis and Dr Anne-Marie Glenny, who have given me the time, knowledge and constructive criticism I needed to complete this thesis, and helped me develop as a researcher. I am forever indebted to them for the help and kindness they have provided me.

Thanks to Dr Malcolm Campbell for educating me in the importance of statistics, and providing statistical support for the feasibility study.

Thanks to all the members of the CCLG and the Cochrane Oral Health Group for sharing your advice and wisdom; in particular thanks to Professors Helen Worthington, Jan Clarkson and Faith Gibson.

I would like to thank my fellow PhD students Lois Orton and Karen Mclean (née Black) for their cake, tea and empathy. Congratulations to Lois for getting there first; Karen, your day will come soon!

Dr Fiona Crawford was unfailingly generous in letting me share her home (and cat) during the most difficult phase of my studies. I am forever grateful for your calm advice, sense of perspective, and fridge full of wine and cheese.

Thanks to all my friends in London, in particular Vic Coombs, Sophie Osborn, Duncan Higgs, Jane Bradley, Oliver Scanlan, Katie Coyle, Hannah Scott, Jen Brookbanks, Becky Rangecroft, Robert Henderson and Tom Buttle: thanks for making moving to London feel like moving home.

Thanks to my sisters Kirsty and Robyn, brother Scott, and brother in law Peter Rayner for your love and support. In particular, thanks to Kirsty for being my tame statistician.

My fiancé Paul Clegg had always been there for me; his unstinting generosity, his motivating words, his reassurance, his sense of humour and his proof reading skills have been invaluable. I can't wait till 6th August 2011.

Finally, my parents, Carol and Glenn Bryan have been unfailingly generous; their loving support throughout my academic career has kept me going. I'd never have got this far without you.

Chapter 1 Introduction

1.1 What is cancer?

Cancer is a class of disease in which cells multiply uncontrollably, giving rise to tumours. These tumours may be benign or malignant. Benign cells are not cancerous because they do not spread to other sites in the body, while malignant cells have the ability to spread, leading to the destruction of the surrounding tissue. These cells can also proliferate to other parts of the body through the blood or lymphatic system, in a process called metastasis (Macmillan, 2010a). There are over 200 types of cancer, of which approximately 85% are carcinomas: cancers of the epithelium. Among the most common of these type of cancers are carcinomas of the breast, lung, prostate and bowel (Macmillan, 2010a). In contrast, leukaemia and lymphoma, cancers of the blood and lymph glades, account for approximately 6.5% of all types of the disease; while sarcomas, cancers of the bone, muscle and fatty tissue, account for approximately 1% (Macmillan, 2010a). The remaining 7.5% of cancer incidence is comprised of a variety of rarer cancers, including brain tumours and multiple myeloma.

Haematological malignancies are cancers affecting the lymph nodes, blood and bone and include leukaemia, lymphoma and multiple myeloma (Lichtman, 2008). The proliferation and infiltration of leukaemia cells into tissue disturbs cell and metabolic function, and results in anaemia, neutropenia, thrombocytopenia, haemorrhage and infection (Bratt-Wyton, 2000). There are two types of leukaemia: chronic and acute. Acute diseases are characterised by their sudden onset. The most common types of acute leukaemia are acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL) (Bratt-Wyton, 2000). ALL is most prevalent in children aged between two and seven years old, although adults over 40 years old are also commonly affected (Bratt-Wyton, 2000). In contrast to these acute diseases, chronic leukaemias are slower to develop. Chronic myeloid leukaemia (CML) and chronic lymphoblastic leukaemia (CLL) are common types of this disease (Bratt-Wyton, 2000).

Lymphoma cells infiltrate tissue, bone marrow and organs, leading to the destruction of healthy tissue. Although the typical site of involvement is the lymph nodes, tissue

without nodes can also be affected. Lymphomas can be separated into two distinct types: Hodgkin's disease (HD) and non-Hodgkin's Lymphoma (NHL). NHL can be additionally separated into low-grade and high-grade lymphoma (Grundy, 2000). Low grade disease is slow growing and asymptomatic, and as a consequence, patients are not generally diagnosed until their disease is at a late, and incurable, stage. Untreated high grade disease is rapidly terminal. However, tumours can be responsive to chemotherapy, if caught early enough (Grundy, 2000). In contrast the incidence of disease-free survival with NHL can be as high as 85% in patients with stage one and two disease (Grundy, 2000).

Multiple myeloma (MM) is an incurable malignancy characterised by uncontrolled plasma cell growth, resulting in the infiltration of plasma cells into bone and the development of osteolytic lesions. The excessive secretion of abnormal immunoglobulins is a characteristic of this disease, however, a rare non-secretory form of the disease does also exist (Dowling, 2000). Patients with MM commonly suffer renal failure as a consequence of hyperviscosity syndrome, an abnormal viscosity of the plasma, or hypercalcaemia, which is caused by the release of calcium into the blood due to bone destruction. Spinal cord compression may also be a consequence of myeloma (Dowling, 2000). Despite treatment, patients inevitably relapse with myeloma. Although new drug regimes have increased the number of patients achieving a complete or very good remission, relapse after first line therapy can be expected within two or three years of diagnosis (Kumar, 2010).

1.2 Treatment for cancer

Treatment for cancer usually involves chemotherapy, radiotherapy, hormone therapy, biological therapy, or surgery, either as a single therapy or in combination (Davies and Epstein, 2010). Transplantation with stem cells, or bone marrow, is another method of treatment, which is commonly used in haematology patients (Blazar et al., 2006).

1.2.1 Chemotherapy

Chemotherapy can be administered, either singularly or in combination, with the intention of cure, for the prolongation of life, or for palliation (Peterson and Lalla, 2010) The synthesis and function of deoxyribonucleic acid (DNA) is altered by the administration of chemotherapy drugs (Bratt-Wyton, 2000), which can be given either intravenously, orally or by injection, in cycles, often over a number of months. Chemotherapy may be separated into four distinct types: alkylating agents, anti-tumour antibiotics, plant alkaloids and anti-metabolites (Thomson, 2000). Alkylating agents form molecular bonds with DNA, causing cross-breaking, substitution or strand breaking reactions, which bring about cell death (Skeel, 2006). Alkylating agents also prevent the formation of ribonucleic acid (RNA) (Thomson, 2000). Melphalan and cyclophosphamide are alkylating chemotherapies commonly used in the treatment of myeloma (Dowling, 2000). Anti-tumour antibiotics, which include doxorubicin and bleomycin, are produced from species of fungus (Thomson, 2000). These drugs affect the synthesis and functioning of DNA and RNA (Skeel, 2006). Anti-metabolite chemotherapies interfere with the synthesis of purine and pyrimidine (Thomson, 2000), and, after they have been incorporated into metabolic pathways, transmit false messages which prevent the synthesis of DNA and RNA (Ingwersen, 2001). Methotrexate is an anti-metabolite chemotherapy used in the treatment of a range of different cancers, including ALL (Bratt-Wyton, 2000). Plant alkaloids are cell cycle specific drugs which interrupt metaphase by crystallizing the microtubular proteins (Ingwersen, 2001, Thomson, 2000). Vinblastine and etoposide are common plant alkaloids (Ingwersen, 2001).

1.2.2 Radiotherapy and TBI

Radiotherapy uses ionising radiation to eliminate tumour cells (Spreadborough and Read, 2000), and can be given externally, whereby daily fractions of radiotherapy are directed towards the tumour; or internally, either through the application of radioactive material into the tumour (brachytherapy), or through radioisotope treatment whereby the treatment is drunk or injected into the body (Macmillan, 2010a). The amount of radiotherapy given is measured in gray (GY); in patients with head and neck cancer, this therapy generally administered on an outpatient basis, with the patient attending daily weekday appointments during the six week therapy cycle. The administration of high dose radiotherapy to the entire body is termed total body irradiation (TBI)

(Spreadborough and Read, 2000). As TBI can penetrate the central nervous system, unlike chemotherapy, it is employed in conjunction with chemotherapy in patients undergoing transplantation (Spreadborough and Read, 2000).

1.2.3 Transplantation

Haematopoietic stem cell transplantation, a term which is often used interchangeably with bone marrow transplantation (and hereafter abbreviated as BMT), involves the administration of stem cells to patients who have been pre-treated with high-dose chemotherapy or a combination of chemotherapy and TBI. In this process cancer therapy is used to destroy the patient's bone marrow and the patient is then 'rescued' using stem cells. These stem cells are either previously harvested from the patient after the administration of growth factors to boost the amount of stem cells circulating in the blood, or harvested in the same manner from another individual who has been identified as a 'match' to the patient. The administration of the patient's own stem cells is termed autologous transplant, while the use of donated cells is called allogeneic transplant (Outhwaite, 2000). Previous to the use of stem cells, bone marrow was harvested from patients during a surgical procedure and used in a similar manner to stem cells transplant. Bone marrow harvesting may still be employed when a patient has trouble producing enough stem cells to harvest, or alternatively when the donor chooses to donate bone marrow rather than stem cells. Some patients may receive a mixed transplant of both bone marrow and stem cells due to problems collecting enough stem cells. BMT is an inpatient procedure, in which patients are hospitalised for up to four weeks.

The administration of chemotherapy, with or without TBI, before transplantation is termed conditioning. This procedure lasts approximately a week in allogeneic transplant patients and one or two days for patients receiving an autologous transplant. The term 'day 0' is used to denote the day a patient receives their transplant (Outhwaite, 2000). The days before transplantation, during which the patient receives myeloablative treatment, are denoted with a minus sign (day-3, day-2, day-1 etc.) and the days immediately after transplantation being designated a plus sign (day+1, day+2, day+3 etc.). Due to the risk of infection, all BMT patients are barrier nursed in private rooms during hospitalisation and medical staff and visitors undergo infection control

procedures, which include hand washing and the donning of protective clothing before entering the room.

1.3 Side effects of cancer treatment

Advances in the cancer treatments have led to increased patient survival though the use of new, highly toxic regimes. However the administration of these new treatments have also increased the incidence of toxicities, or side effects, associated with their use (Jones et al., 2006). The nature and scale of these side effects are diverse, and may not be experienced by all patients undergoing therapy. Common side effects include myelosuppression which increases the patient's risk of infection, alopecia, nausea and vomiting, gastrointestinal mucositis, oral complications, fatigue, reproduction issues and damage to major organs in the body, such as the heart. Oral complications include oral infection, salivary gland dysfunction, hyposalivation, haemorrhage, compromised wound healing, taste disturbances, osteonecrosis, necrosis and fibrosis of the soft tissues, possible induction of secondary malignancy and oral mucositis (OM) (Davies and Epstein, 2010).

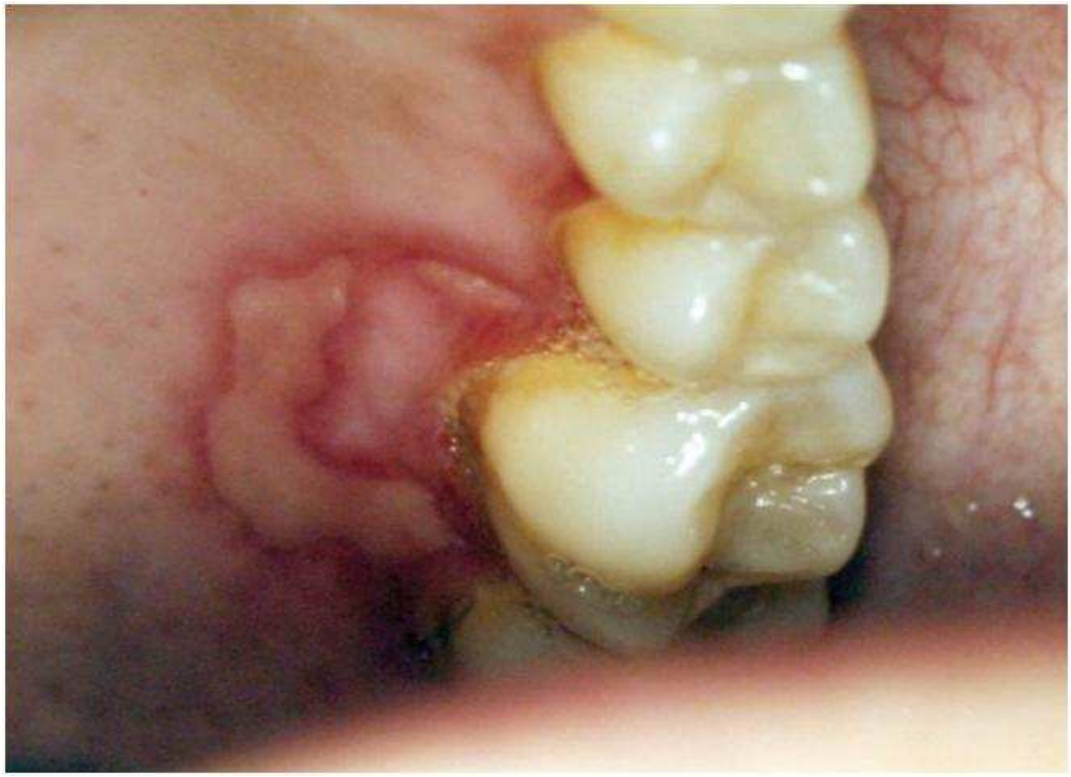


Figure 1: Clinical Presentation of Oral Mucositis

(Scully 2006. Permission granted)

Mucositis is an inflammatory and frequently ulcerative side effect of cancer treatment, which has been identified by patients as the most debilitating aspect of their treatment (Bellm et al., 2000, Stiff, 2001). The incidence of this condition varies depending on the treatment administered and individual patient characteristics. Incidences as high as 100% have been reported in patients receiving radiotherapy for head and neck cancers (Peterson et al., 2009b). OM can be extremely painful for the patient and can have a significant impact on their quality of life by limiting their ability to eat, drink, talk, swallow and sleep. Although patients are generally prescribed opiates for pain control, break-through pain is not uncommon, and the reliance on opiates can introduce additional problems for the patient, due to their sedative effect. OM therefore constitutes a clinically relevant problem, as patients with severe mucositis often require breaks in planned courses of treatment to allow the oral cavity to recover; such breaks can negatively impact tumour control and therefore the patient's overall chance of survival (Rosenthal, 2007). Ulceration also offers a gateway for opportunistic infection, which when combined with nadirs in the white cell count of the patient, can elicit devastating effects (Peterson and Lalla, 2010). Unplanned admissions and extended hospital stays, together with the need for nutritional support and opiates, exert a significant economic impact. As such, the discovery of an intervention which could either prevent or reduce the severity of OM would have a hugely beneficial impact, not only clinically and economically, but also most importantly for the patient's quality of life.

A number of interventions have been investigated for the prevention of mucositis, with mixed results. A recent update of the Cochrane review of interventions for the prevention of mucositis included 130 trials of 43 separate agents (Worthington et al., 2010). However, to date, no intervention has been found to be beneficial for the prevention of mucositis across all treatment modalities. Many of these trials are small and poorly reported. Additional trials are required to confirm these results. Some interventions that have been excluded from the Cochrane review are relatively safe and economical and merit further evaluation. One such intervention is vitamin E. Vitamin E has been previously evaluated in randomised controlled trials (RCTs), the 'gold standard' for assessing the effectiveness of interventions, in the prevention of mucositis in patients undergoing chemotherapy (Sung et al., 2007) and radiotherapy (Ferreira et al., 2004) with conflicting results. Further RCTs would be required to confirm the

effectiveness of vitamin E for the prevention of mucositis. However, before a large scale study of any intervention is conducted, it is advisable to conduct a feasibility study to thoroughly explore the pragmatic aspects of the research project (Easterbrook and Matthews, 1992).

1.4 Overview of this thesis

This thesis combines appraisal of the literature and empirical research, and uses lessons learned from previous studies together with the results of a feasibility study to identify a best practice model for future trials. Figure 2 displays the conceptual diagram for the thesis.

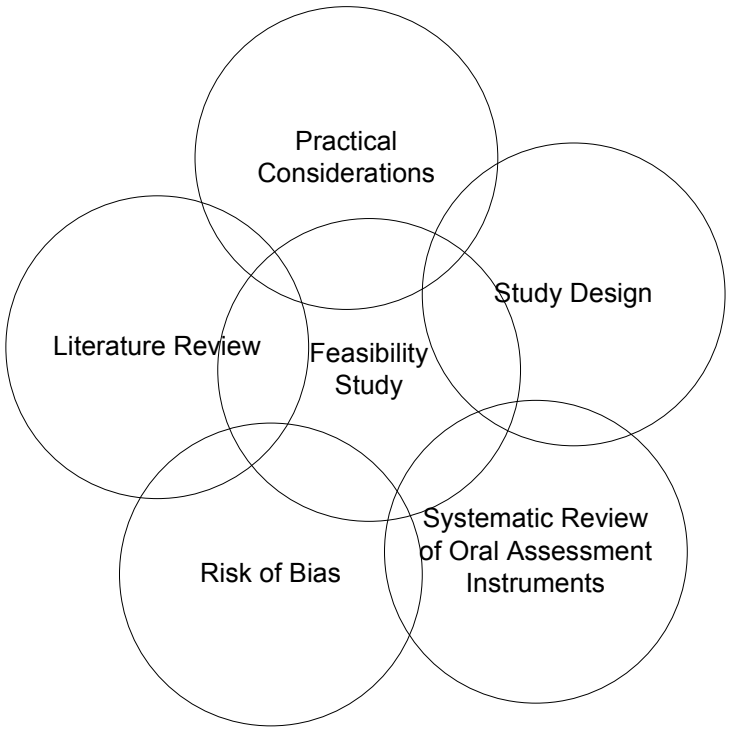


Figure 2: Thesis diagram

Chapter two reviews the literature surrounding mucositis. Sonis' five phase hypothesis for development of mucositis is explained and treatment and patient related factors which may affect the OM incidence or severity are discussed. Such factors are important as the identification of high risk patients allows for better treatment planning and patient education, and the early employment of interventions to treatment pain and associated oral symptoms. The clinical impact of mucositis is then explored: as the development of mucositis increases a patients susceptibility to infection, increases a

patients' length of hospital stay (Sonis et al., 2001, Vera-Llonch et al., 2007a, Vera-Llonch et al., 2007b) and requirement for opiate pain control, and in severe cases may necessitate breaks in treatment to allow for the oral surface to recover. Such treatment breaks may affect the success of treatment (Blijlevens et al., 2009, Epstein and Schubert, 2004, Scully et al., 2006). Consequently therefore, mucositis also exerts a significant economic impact, although the actual costs described may not translate from an American health care model to a British model. Lastly the impact of mucositis on the patient is discussed.

Interventions previously trialled for the prevention of mucositis are discussed in chapter three. This chapter provides a brief outline of the use of RCTs and systematic reviews and then discusses the latest update of the Cochrane review of interventions for the prevention of mucositis (Worthington et al., 2010). Three interventions were identified in this update that were beneficial for the prevention of mucositis at all three levels of interest: cryotherapy in patients receiving chemotherapy, honey in patients receiving radiotherapy, and Keratinocyte GF in a range of different treatments. However, no interventions were found to be beneficial for all treatments, and further research is needed. One drawback of the prevention review is that only studies which provide data in the correct formats can be included, which leads to the exclusion of studies providing data in formats other than the number of patients experiencing each grade of mucositis. Although text only inclusions have been included in the latest update of the review in an attempt to address this issue, this has not prevented whole interventions from being excluded from the review due to the manner in which data were presented or due to the oral assessment instrument employed. One such intervention is vitamin E. The remainder of chapter three discusses the conflicting results of studies which have examined vitamin E for either the prevention or treatment of mucositis.

Chapter four is an empirical piece of research which assesses the risk of bias (ROB) of the studies included in the Cochrane review for the prevention of mucositis (Worthington et al., 2010). A bias is a systematic error in results, which can operate in either direction, leading to an over or underestimation of the effect of the intervention under investigation. All 130 studies included in the latest prevention review were assessed for ROB using the Cochrane ROB instrument. Outcome assessor blinding and

adequate allocation concealment were chosen as the key domains of interest, and a sensitivity analysis was performed in which all studies at high or unclear ROB for these domains were excluded from the prevention review and the results reanalysed. Overall ROB was also determined, and the results of the sensitivity analysis discussed.

Chapter five considers how information from studies identified by the Cochrane prevention review can be used to inform future trials. Recruitment rates were calculated for the 80 studies which provided dates for the start and end of recruitment. Two mean averages were then determined: an overall average and an average for studies conducted on single sites. Next, all 130 studies were examined to determine which other outcomes were reported by the authors. Nineteen categories of outcomes were identified. However, there was little consistency in what studies were reported. Adverse events were the most frequently identified outcome, but were reported by only 47% of the studies assessed for ROB. Patient quality of life was the least frequently reported outcome. The timing of oral assessment was also explored, which again showed little consistency, with a variety of timings employed from daily, twice weekly, weekly, and monthly. Three studies only assessed the oral cavity a total of twice (Li et al., 2006, Pfeiffer et al., 1990, Sorensen et al., 2008). The final section of this chapter examines the pitfalls and problems identified by previous studies. These ranged from recruitment problems and slow accrual of patients into the study, to drug dispensing errors, and difficulty in obtaining the intervention or placebo products used in the study. The use of a feasibility study to identify potential problems is then discussed.

Chapter six presents a systematic review of oral assessment instruments for use in adults, which was conducted in order to select instruments for use in a feasibility study. The results of a systematic search for the update of the Children's Cancer and Leukaemia Group (CCLG) mouth care guidelines (UKCCLG-PONF, 2006) and a subsequent linked publication which aimed to identify oral assessment instruments for use in children (Gibson et al., 2010), were used to determine suitable oral assessment instruments for use in adults. A total of 391 papers were identified in the literature search. Fifty oral assessment instruments were included in the review, of which only 10 had been validated. This chapter goes on to describe instruments in detail and then discuss their various merits and issues before selecting three instruments for use in a

future trial. The instruments chosen were the daily index of mucositis (DIM) (Tardieu et al., 1996), the oral mucositis daily questionnaire (OMDQ) (Stiff et al., 2006), and the World Health Organisation (WHO) instrument (World Health Organization (WHO), 1979).

The feasibility trial protocol is presented in chapter 7. This chapter details the development of the feasibility study and describes the process of finding a supplier for the intervention and placebo products and the need for the repackaging of these products to meet manufacturer's authorisation for investigation medicinal products (MA-IMP) requirements. The MRC frameworks for complex interventions are presented and the use of a phase three design is justified. The inclusion and exclusion criteria are discussed, along with reasons for these decisions. A discussion of the ethical issues applicable to this trial is also included in this chapter along with diagrams which detail the patient experience during allogeneic and autologous transplant.

The results of the feasibility study are discussed in chapter eight. The first part of this chapter describes feasibility issues identified during the trial. The discussion of Clinician interest and the available patient population is probably one of the most important aspects of this section, as the recruitment of patients into the feasibility study was severely affected by a lack of access to patients and by the dynamics of the staff on the ward. A lack of consistency in the standard oral care given to patients is highlighted. The feasibility of the recruitment, consent, randomisation and blinding procedures are also detailed in this section. The second part of this chapter details the results of the study. However, as only nine patients were recruited into the study, the focus of this section is not on the statistical difference between the study arms but rather on the results of individual patients. The oral mucositis outcomes are discussed first and a difference between the DIM and WHO oral assessment instruments was identified. The data produced using the pain scales, nutritional screening instruments, and the adverse events recorded during the study are then reported.

Chapter nine presents the discussion which considers the findings of the feasibility study together with the findings of the other chapters in this thesis. Barriers to

recruitment of patients and the need for Clinician input into trial design are important topics discussed in this chapter, as these issues adversely affected the success of recruitment in the feasibility study. The feasibility of the method of allocation concealment and outcome assessor blinding employed in this study are considered and the importance of the use of these domains in future trials, in particular those in which patient blinding is unfeasible, are discussed. The time required for adverse event reporting and the problem of ensuring accurate reporting of adverse events after patients have been discharged are also talked about in detail. Finally recommendations for future trials are made. The conclusion of this thesis is presented in Chapter ten.

Chapter 2 Literature Review

2.1 Introduction

This chapter provides the background to the thesis. The first section begins by focusing on OM development, and then subsequently on the amelioration and exacerbation of this condition by various patient and treatment factors, before finally considering the greater impact of mucositis on patients and resources. The second section of the literature review focuses on interventions for the prevention of mucositis.

2.2 Incidence and development of mucositis

The incidence of OM varies depending on the type of treatment the patient receives. Mucositis has been reported in between 40% and 79% of patients receiving standard chemotherapy (Cascinu et al., 1994, Nottage et al., 2003, Okuno et al., 1999, Ramirez-Amador et al., 2010) and between 60% and 100% of patients with head and neck cancer receiving radiotherapy (Cengiz et al., 1999, Makkonen et al., 1994, Trotti et al., 2003). In patients undergoing bone marrow or stem cell transplants the incidence is much higher, with between 76% and 100% of patients developing some degree of mucositis (Blazar et al., 2006, Castagna et al., 2001, Lilleby et al., 2006, McGuire et al., 1993, Salvador, 2005, Spielberger et al., 2004, Vera-Llonch et al., 2007a, Wardley et al., 2000), and between 66% and 76% of patients developing severe mucositis (Bolwell et al., 2002, Wardley et al., 2000, Woo et al., 1993).

The direct mucotoxic effects of chemotherapy usually starts to be seen at four or five days post therapy with the reddening of the mucosa, a process called erythema (Scully et al., 2006). Ulceration starts to develop between seven and 11 days after chemotherapy (Ramirez-Amador et al., 2010, Scully et al., 2006, Woo et al., 1993). In the absence of infection, OM generally begins to resolve between days 14 and 17 (Scully et al., 2003, Woo et al., 1993). The development of mucositis varies depending on the type of treatment received. Mucositis induced by chemotherapy commonly takes place on the non-keratinized mucosal surfaces of the mouth, including the soft palate, buccal mucosa, floor of the mouth and tongue (Scully et al., 2003). Surfaces with higher levels of keratinization have a greater resistance to trauma (Schubert, 1993), and therefore erythema and ulcers usually appear on the gingivae (gums) later in mucositis

development. In a longitudinal study of 59 patients undergoing BMT, Woo and colleagues found that 96% of observed oral lesions were located on non-keratinized surfaces, with the buccal mucosa, floor of the mouth and the ventrolateral tongue being the sites most frequently involved (Woo et al., 1993). Ulceration of the hard palate is rare in patients receiving chemotherapy, and in the bone marrow transplant patient may be attributed to herpes simplex virus (HSV) (Scully et al., 2006) or graft-versus-host disease, a side effect of the transplant process (Woo et al., 1993).

Unlike mucositis induced by chemotherapy, radiation-induced mucosal damage in head and neck patients can take place anywhere within the radiation field, affecting both the keratinized and non-keratinized surfaces (Scully et al., 2003), with the most common areas of involvement being the lateral and ventral aspects of the tongue, the buccal mucosa and the soft palate (Treister and Sonis, 2007). Pain and erythema are generally the first signs of radiation mucositis which tend to begin at doses of around 10 GY, typically at the end of the first week of treatment (Treister and Sonis, 2007). Mucositis commonly becomes ulcerative at doses of 30 GY (Scully et al., 2003), and a pseudomembrane, a fibrous layer on the surface of the mucous membrane, may develop. In the absence of infection, spontaneous healing normally starts approximately two weeks after the completion of treatment (Treister and Sonis, 2007). In contrast to chemotherapy-induced mucositis, which has a relatively short duration, it is common for patients receiving radiotherapy for head and neck cancers to suffer from ulcerative mucositis which persists for up to four weeks following treatment completion (Sonis, 2009).

2.3 Models of mucositis

Until relatively recently, the principal theory of mucositis development was that chemotherapy or radiotherapy caused the indiscriminate destruction of stem cells located in the basal epithelium of the oral cavity, inhibiting cell turnover and resulting in ulceration (Barasch and Peterson, 2003, Logan et al., 2007, Sonis, 2009). However in 1998, Sonis put forward a new hypothesis for mucositis development which proposed a more complex sequence of events (Sonis, 1998). This model initially involved four phases: the inflammatory-vascular phase, the epithelial phase, the ulcerative phase and the healing phase (Sonis, 1998). In 2004, the model was expanded to incorporate a fifth

phase. The model currently comprises: the initiation phase, the upregulation and message generation phase, the signal amplification phase, the ulceration phase and the healing phase (Sonis, 2009) (Figure 3).

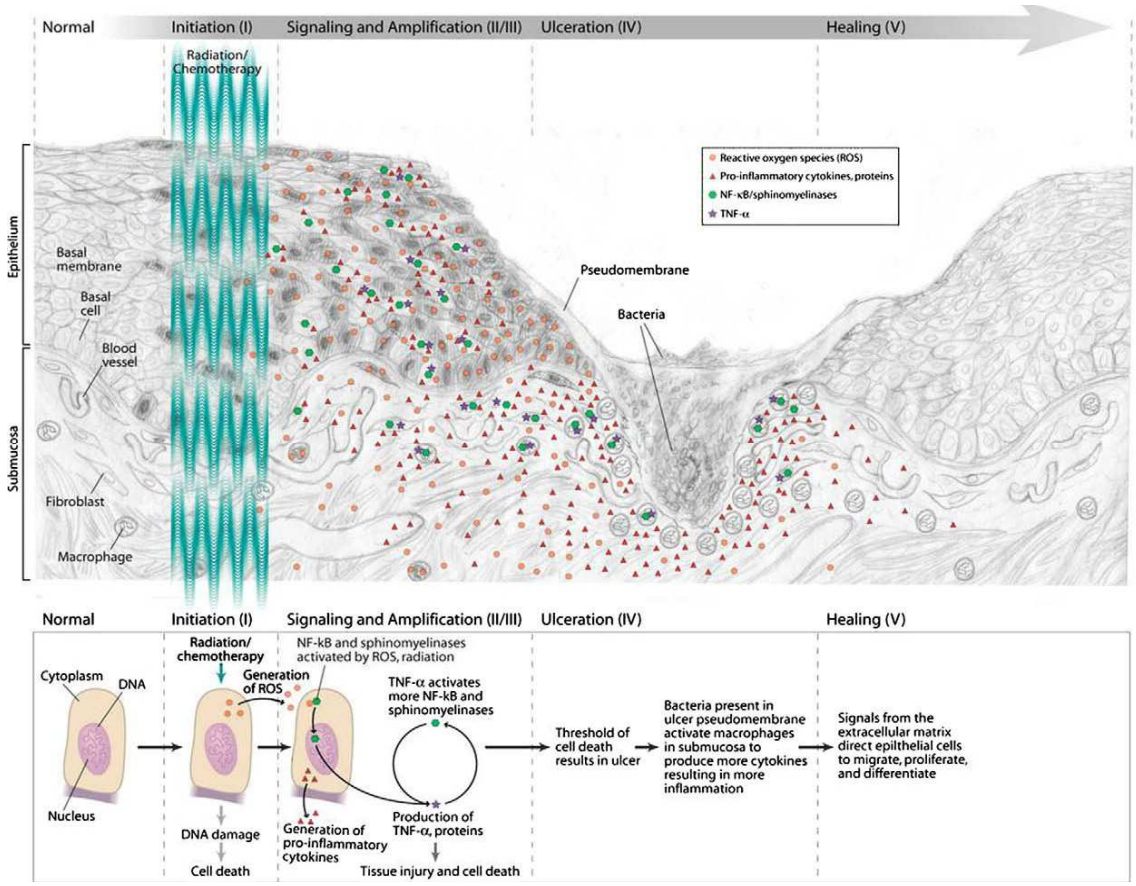


Figure 3: The Five Phase Model of Mucositis

(Sonis 2009. Permission granted)

During the initiation phase, chemotherapy or radiotherapy-induced DNA strand breakage results in clonogenic death of cells in the basal epithelium (Sonis, 2009). Direct mucosal damage also results from the generation of reactive oxygen species (ROS) (Logan et al., 2007, Sonis, 2004). In the second phase of Sonis' model DNA stand breakages and lipid peroxidation trigger the production of transcription factors, including the tumour protein p53 and nuclear factor-κB (NF-κβ), through transduction pathways. NF-κβ has an important role in the body's inflammatory response, eliciting both pro-inflammatory and anti-inflammatory processes depending on at which point the pathway is stimulated (Logan et al., 2007). NF-κβ is responsible for the upregulation

of approximately 200 genes including: pro-inflammatory cytokines (tumour necrosis factor (TNF)), interleukin-6 (IL-6) and interleukin-β (IL-β), cell adhesion molecules, immunoreceptors, acute phase proteins, cell surface receptors and stress response genes. Such genes affect mucosal integrity by inducing cell death, tissue damage and apoptosis (Logan et al., 2007). Radiation and chemotherapy also target fibroblasts within the submucosa during this phase, through the activation of matrix metalloproteinase 3 (MMP3) by cyclooxygenase-2 (COX-2) (Logan et al., 2007). MMP3 breaks down the basement membrane of the epithelium, and helps destructive signal promotion (Sonis, 2004).

Sonis's third stage is the 'signal amplification phase.' This stage involves both direct damage to cells, and the continuation and amplification of the proinflammatory cytokine initiated processes (Cawley and Benson, 2005), through positive or negative feedback loops (Sonis, 2009). For example, TNF production leads to an increase in production of NF-κβ, which in turn leads to the increased production of TNF (Sonis, 2009). TNF is a pleiotropic protein which has a role in the inflammatory immune response (Logan et al., 2007). TNF instigates cell death by disrupting cytotoxic inflammation, blood flow, and immune response regulation (Rieger, 2001). Many of these mechanisms occur simultaneously. Sonis recently used the metaphor of airline flight maps to explain the inter-related mechanisms at action during this phase, and how busy hubs (major cities) and outlying nodes can get overwhelmed when busy. This deadlock prevents intermittent resolution of the inflammatory cascade, and results in the fourth phase: 'ulceration'(Sonis, 2009).

The 'ulceration phase' takes place between days ten and 15 post-treatment. This stage shows the most overt clinical signs of mucositis, with the presence of deep ulcers, and on occasions a pseudomembrane (Cawley and Benson, 2005). The breakdown in mucosal integrity introduces avenues for the entry of bacteria, and this can result in the development of sepsis (Sonis, 2004). Data from animal models shows that during the transition between intact mucosa and ulceration, the number of mucosal bacteria increases over 300 times (Sonis, 2009). The penetration of the submucosa by products of these colonizing bacteria, together with the penetration of cell wall products such as lipopolysaccharides and cell wall antigens (Sonis, 2009), promote further damage, by

initiating the production of additional cytokines (Logan et al., 2007, Sonis, 2004). This is especially damaging in the neutropenic patient, as sepsis or bacteraemia may result if bacteria invades the submucosa (Sonis, 2009)

The fifth and final stage of this model is the 'healing phase' (Sonis, 2004). This is the least understood phase in the model (Logan et al., 2007). During this phase the epithelial cells that surround the ulcer proliferate into the wound, and start to form layers. This process is stimulated by extracellular matrix signalling from the submucosa (Sonis, 2009). Crucially, cells located below the mucosal surface remain damaged, never fully returning to their previous condition, increasing the risk of future trauma (Cawley and Benson, 2005).

2.4 Factors affecting mucositis development

The identification of factors which increase a patient's risk of developing mucositis is beneficial for use in both clinical practice and research. Patients most at risk of developing severe mucositis can be identified before treatment and early interventions employed. Such factors can also be used to stratify patients in clinical trials in order to balance the treatment arms, and such factors can be controlled for in *post hoc* analyses. Various studies have attempted to identify the factors affecting mucositis development. Fourteen of these studies have used multivariate analysis. This method of statistical analysis allows the identification of the contribution of individual risk factors in the development of an outcome, in this case oral mucositis, and eliminates the influence of confounding variables (Katz, 2003). The studies using this method of analysis are shown in Table 1. The studies identified were conducted in three different populations. The majority of studies identified factors affecting mucositis development in patients undergoing autologous or allogeneic transplantation (Blijlevens et al., 2008, Bolwell et al., 2002, Grazziutti et al., 2006, Mattsson et al., 2006, Ohbayashi et al., 2008, Robien et al., 2004, Salvador., 2005, Vokurka et al., 2009, Wardley et al., 2000). Three studies were performed in chemotherapy patients (Cheng et al., 2008, McCarthy et al., 1998, Schwab et al., 2008), and only one study was identified in radiotherapy patients (Elting et al, 2007). Twenty-six factors affecting mucositis severity were identified. These can be separated into treatment related and patient related factors, and will be used to inform

the backbone of the next section of this review. Where relevant, studies not employing multivariate analyses will be used as secondary levels of evidence.

Table 1: Studies Using Multivariate Analysis to Identify Factors Affecting Mucositis Development or Intensity

Author	Patient Characteristics	Condition and treatment	Chemotherapy	Risk factors included in analysis	Results	Comment
Chemotherapy						
Cheng et al, 2008	82 Paediatric patients	Chemotherapy patients.	Vincristine, etoposide, doxorubicin, Daunorubicin, methotrexate, cytarabine, melphalan, cyclophosphamide.	Gender, pre chemotherapy weight, height and BMI, pre-existing dental problems, nadir neutrophil count, peak AST/ALT, peak creatinine, peak nausea and vomiting, use of cytokines, use of multi-vitamins,	Lower body weight (P=0.0013) Lower value of log nadir neutrophil count (P=0.0025) Higher value of peak creatinine (P=0.025).	
McCarthy et al, 1998	63 patients 34M/ 29F	Chemotherapy patients	5-Flurouracil	Gender, diagnosis of diabetes, age, use of prostheses, education, BSA, smoking status, consumption of alcohol, use of prescription drugs, salivary flow rate, plaque index, use of medication for xerostomia, presence of xerostomia, patient reports of oral problems at baseline, performance status, cytotoxic regimen, chemotherapy by continuous infusion, baseline neutrophil count, baseline white cell count and presence of herpes simplex virus antibody	Xerostomia at baseline (OR=10.0, P=0.04) Baseline neutrophil count below 4000 cells /mm^3 (OR=3.9, P=0.0355)	Prospective study

Author	Patient Characteristics	Condition and treatment	Chemotherapy	Risk factors included in analysis	Results	Comment
Schwab et al, 2008	683 patients 383M/300F	Chemotherapy	5-Flurouracil	Gender, creatine levels, genotypes (DPYD, TYMS, MTHFR), diarrhoea, leucopoenia, use of folinic acid, mode of chemotherapy administration.	Female gender (OR, 2.37; 95% CI, 1.32 to 4.26, P=0.0036) DPYD*2A allele (OR, 58; 95% CI 1.71 to 19.4, P=0.013)	Studied treatment related toxicities associated with 5-FU. Not only mucositis.
Transplantation						
Blijlevens et al, 2008	197 patients 113M/ 84F	Autologous transplant	Melphalan 200mg/m^2, or carmustine 300mg/m^2, etoposide 800mg/m^2, cytarabine 800 to 1600mg/m^2 or melphalan 140mg/m^2	Age, BSA, weight, height, performance status, chemotherapy type and dose.	<u>Determinants of severe OM incidence:</u> Melphalan dose per kg body weight (MM patients) (P<0.001), Carmustine dose per kilogram of body weight (NHL patients) (P<0.001), ECOG performance status (P=0.013) <u>Determinants of severe OM duration:</u> Melphalan dose in MM patients (P=0.009) Carmustine dose in NHL patients (P=0.006)	Multi-site study (25 centres in 13 EU countries). Prospective study.

Author	Patient Characteristics	Condition and treatment	Chemotherapy	Risk factors included in analysis	Results	Comment
Bolwell et al, 2002	79 patients, 56M/23F	Autologous stem cell transplant patients	Busulfan, cyclophosphamide and etoposide or busulfan and cyclophosphamide. Two patients received other regimes	Gender, age, actual body weight, ratio of actual body weight to ideal body weight, chemotherapy courses, conditioning regimen, mobilization regimen, diagnosis, prior radiation.	Prior radiation therapy (P=0.001), Diagnosis of NHL (P=0.007), Mobilisation with etoposide (P=0.034)	Diagnosis was significant in univariate analysis but did not reach significance in multivariate analysis. Prospective study
Grazziutti et al, 2006	381 consecutive patients 235M/146F	Autologous transplant	Melphalan	Age, race, weight, BSA, BMI, liver and renal function, melphalan dose, serum albumin, gender.	Severe Mucositis predictors: High serum creatinine (OR=1.581; 95% CI: 1.080-2.313, P=0.018) Higher Melphalan dose per kg/bodyweight (OR=1.595; 95% CI: 1.065-2.389; P=0.023)	Higher alkaline phosphatise also identified in univariate analysis
Mattsson et al, 1991	205 consecutive allogeneic BMT patients, 127M/78F	Allogeneic patients	Cyclophosphamide or cyclophosphamide with TBI.	Age, gender, conditioning with TBI, GVHD prophylaxis, prolonged aplastic period, number of HLA matches, bone marrow dose $<3x10^8$, herpes simplex virus, septicaemia,	Bone marrow dose $<3x10^8$ cells/kg (P<0.0001), prolonged aplastic period (WBC count $<0.2x10^9$ cells/l) for more than 14 days (P<0.005), HSV-seropositive recipients (P<0.01), Conditioning with TBI (P<0.02),	Age and GVHD prophylaxis with methotrexate were significant in univariate analysis

Author	Patient Characteristics	Condition and treatment	Chemotherapy	Risk factors included in analysis	Results	Comment
Ohbayashi et al, 2008	96 patients	Allogeneic transplant	Cyclophosphamide / TBI, busulfan / cyclophosphamide	Recovery of WBC count, age, date of transplant, oral health care, conditioning regime, source of donor (related/unrelated), use of oral cryotherapy, diagnosis, gender, type of graft, number of HLA mismatches, incidence of severe GVHD, risk (high / low)	Conditioning regime (P=0.003) Oral health care (P=0.024)	Conditioning regime, age, donor source, oral health care and date of transplant all significant in univariate analysis.
Robien et al, 2004	133 patients	Allogeneic stem cell transplant patients	Cyclophosphamide /TBI or busulfan / cyclophosphamide	Gender, race, age, weight, height, BMI, BSA, treatment with interferon-alfa, smoking history, conditioning regimen, relationship of donor, source of stem cells, compatibility of patient with donor, incidence of graft versus host disease, date of transplant, use of growth factors and ganciclovir, length of time between diagnosis and transplant, hydroxyurea, use of cytarabine and busulfan, use of methotrexate, use of multi-vitamins,	Conditioning regimes including TBI (P<0.01) BMI>25 (P<0.01) MTHFR 677TT Genotype (P=0.01) Pretransplant multivitamin supplementation (P=0.04) Current smoking (P=0.04)	Smoking result based on only 4 patients.
Salvador 2005	140 patients 84M/54F	Autologous stem cell transplant patients	Melphalan, or etoposide and melphalan.	Age, gender, diagnosis, cytotoxic regimen, serum creatinine level, BMI, level of prevention,	Peak creatine (P=0.0436) Chemotherapy protocol (P=0.0042) Diagnosis (P=0.0042) Level of prevention (P=0.0181)	

Author	Patient Characteristics	Condition and treatment	Chemotherapy	Risk factors included in analysis	Results	Comment
Vokurka et al, 2006	148 patients BMT, 94M/54F	Autologous stem cell transplant patients	BEAM or melphalan chemotherapy	BMI, cytotoxic regime, mouthwash solution, number of cells in the graft, age, gender,	Female gender Melphalan administration	Short report. No figures given for multivariate analysis.
Vokurka et al, 2009	101 patients 53M / 48F	Allogeneic stem cell transplant patients	Busulfan and cyclophosphamide fludarabine and Melphalan	Age, cytotoxic regimen, gender, BMI, number of HLA matches, type of graft, number of cells in the graft, methotrexate dose, creatinine clearance, history of mucositis, diabetes, use of oral prosthesis, use of filgrastim, time since last chemotherapy administration, bilirubin levels,	Melphalan dose per kg of bodyweight (P=0.0083) Melphalan dose (per kg bodyweight) also a predictor of severe mucositis (P=0.0086)	Female gender was significant in a univariate analysis.
Wardley et al, 2000	429 patients 270M/159F	Mixed autologous and allogeneic transplant patients	Cyclophosphamide and Busulfan, Cyclophosphamide and TBI, Carmustine, Cyclophosphamide, etoposide and carmustine, Melphalan, Melphalan and TBI.	Cytotoxic regimen, type of cells, use of growth factors, age, gender,	Conditioning regime (P<0.00005)	Myeloablative regime, haematopoietic progenitor source, use of myeloid growth factors, and age were all significant in a univariate analysis.

Author	Patient Characteristics	Condition and treatment	Chemotherapy	Risk factors included in analysis	Results	Comment
Radiotherapy						
Elting et al, 2007	204 patients 159M/45F	Head and Neck patients	Mean RT Dose (Grays)=67 63 patients received altered fractionation.	Age, gender, diabetes, use of chemotherapy, use of intensity-modulated radiotherapy, use of altered fractionation, type of cancer, oral health	<u>Determinants of OM (all grades) duration:</u> Chemotherapy use (P<0.001) Oral cavity or oropharynx primary (P<0.001) <u>Determinants of severe OM (grades 3/4) duration:</u> Oral cavity or oropharynx primary (P<0.001) Altered fractionation schedules (P=0.04) <u>Risk of grade 3 or 4 mucositis duration</u> Oral cavity or oropharynx primary (OR, 9.4 95%CI 47.1-21.8, P<0.001) Diabetes (OR, 6.6 95% CI 1.3-34.1, P=0.02 Altered fractionation schedules (P=0.002)	

AOR=Adjusted Odds Ratio, AST=aspartate aminotransferase, ALT=alanine aminotransferase, BEAM=Bischloroethyl nitrosourea etoposide ara-c melphalan, BMI=Body mass index, BSA=Body surface area, CI= Confidence Intervals, EU= European Union, F=Female, GVHD=Graft versus host disease, HLA=Human leukocyte antigen, KG=Kilogram, M=male, MEL=Melphalan, OR=Odds Ratio RT=Radiotherapy, TBI=Total body irradiation, WBC= White blood cell,

2.4.1 Therapy related factors

2.4.1.1 Chemotherapy regimes

Wardley and colleagues (2000) identified conditioning regimens as the only factor affecting mucositis development using a multivariate analysis. In this study melphalan, an alkylating chemotherapy, was associated with the greatest incidences of mucositis in an analysis of 429 patients receiving a variety of chemotherapy regimens while undergoing transplantation (Wardley et al., 2000). Melphalan administration was also identified as a risk factor by Vokurka and others (2006), who studied 148 patients receiving chemotherapy with either melphalan or a combination of carmustine, etoposide, cytarabine and melphalan chemotherapy (BEAM) (Vokurka et al., 2006).

Three studies identified melphalan dose per kilogram (kg) of bodyweight as a determinant of severe mucositis (Blijlevens et al., 2008, Grazziutti et al., 2006, Vokurka et al., 2009). Melphalan dose is normally calculated based on the patient's body surface area. This can result in a wide variation in the actual dose a patient receives (Grazziutti et al., 2006), and as a consequence lighter patients may receive a higher dose of chemotherapy than necessary. Blijlevens and others have hypothesised that the difference between the body surface area dose and the per kilogram dose may explain why low body weight and female gender have been identified as risk factors for OM development, as these patients tend to receive high doses of chemotherapy per kilogram of their body weight (Blijlevens et al., 2008). The identification of high peak creatinine levels as a risk factor for mucositis development by two studies (Cheng et al., 2008, Salvador, 2005) is notable as melphalan administration is associated with an increased risk of nephrotoxicity. It therefore appears that this decrease in kidney function may result in a delay in the elimination of chemotherapy agents, and therefore an increase in mucosal damage.

Other chemotherapy drugs that have been suggested to exhibit higher incidences of mucotoxicity include 5-fluorouracil (5-FU), cisplatin, etoposide, methotrexate, taxanes (docetaxel and paclitaxel), melphalan, cytarabine, vinblastine and doxorubicin (Ramirez-Amador et al., 2010, Robien et al., 2004, Scully et al., 2003). In addition to exhibiting direct mucosal effects, etoposide and methotrexate are cell cycle specific

drugs which are excreted in the saliva, which possibly explains the increased mucotoxicity associated with these drugs (Avritscher et al., 2004, Pico et al., 1998). In addition to the type of chemotherapy administered, the method of administration may affect mucositis severity. Damon et al (2004), conducted an RCT comparing the levels of toxicity in patients receiving etoposide as a bolus infusion compared to those receiving the drug by continuous infusion, and reported that the continuous infusion group experienced significantly more mucositis than patients in the bolus group (Damon et al., 2004).

2.4.1.2 Radiotherapy regimes

Only one study identified employed a multivariate analysis to identify risk factors for mucositis development in radiotherapy patients (Elting et al., 2007). The use of concomitant chemotherapy was identified as a determinant of mucositis development in this study; whereas, the use of altered fractionation schedules were identified as a determinant of severe mucositis (grades three and four). Primary site of cancer in the oral cavity or oropharynx were identified as a determinant in both categories (Elting et al., 2007). The suggestion that patients with cancer of the oral cavity or oropharynx may experience more mucositis and mucositis of a greater severity is logical given that the oral cavity of these patients will receive large doses of radiotherapy directly to the mucosa.

The use of altered fractionation: (the use of hyperfractionated regimes in which the dose a patient receives during each radiotherapy schedule is reduced but the number of sessions is increased) or the use of concomitant boost (the introduction of extra radiotherapy sessions per day at the same dosage), increases the risk of mucositis because the total dose of radiotherapy a patient receives may be increased and the timescale of the therapy reduced. Elting and colleagues' (2007), findings are supported by the results of the continuous hyperfractionated accelerated radiotherapy (CHART) trial which compared hyperfractionated to conventional radiotherapy in 918 patients with head and neck cancer. and reported that patients receiving hyperfractionated regimes experienced mucositis of higher incidence and longer duration (Bentzen et al., 2001). However, the authors also report that resolution of confluent mucositis was

quicker in the patients receiving hyperfractionated therapy, which is a notable result (Bentzen et al., 2001).

2.4.1.3 Combinations of chemotherapy and radiotherapy

Patients undergoing BMT may also receive TBI. There is currently no consensus in the published data on the mucotoxicity of chemotherapy regimens when combined with TBI (Avritscher et al., 2004). Mattsson and colleagues (1991), prospectively studied 205 allogeneic BMT patients. Patients were treated with either cyclophosphamide or a combination of cyclophosphamide and TBI. Unfortunately, the authors are vague about the number of patients who received each protocol. Mucosal lesions developed in 148 patients, 138 of whom had received TBI. In a multivariate analysis, treatment with TBI was identified as a risk factor for lesion development ($P<0.02$). These findings are supported by the work of Zerbe and colleagues (1992), who conducted a retrospective chart analysis of 20 patients who had undergone transplantation over a two year period. Nine of these patients received busulfan, etoposide and cyclophosphamide conditioning. Another nine patients received TBI with etoposide and cyclophosphamide. The final 2 patients received other protocols (Zerbe et al., 1992). There was a trend towards an earlier onset of mucositis in patients treated with TBI in this study. However, this difference was not statistically significant. Patients treated with TBI also experienced a higher average daily mucositis score, measured using the oral assessment guide (OAG), during the first week of treatment. Significant differences were found between the groups at day 0 ($P=0.0192$), day+2 ($P=0.033$) and day+4($P=0.033$). However, no significant differences between the groups were found either overall, or for the first week data (Zerbe et al., 1992).

Conversely, Woo and colleagues (1993), reported a similar incidence of ulcerative mucositis in nine patients receiving a busulfan and cyclophosphamide (77.8%) compared to 24 patients who received cyclophosphamide and TBI (79.2%) in their longitudinal study. The mean score of mucositis in the patients treated with busulfan was slightly higher, with a score of 2.4, compared with the score of 2.0 in the patients receiving TBI (Woo et al., 1993). These results are supported by data from the prospective study conducted by Wardley (2000), where patients treated with melphalan

experienced mucositis of a greater severity than patients receiving TBI (Wardley et al., 2000).

It is notable that patients receiving a combination of cyclophosphamide etoposide and carmustine or melphalan experienced both a higher incidence and a greater mean severity of ulcerative mucositis than patients treated with TBI. While the potential for the use of TBI to increase mucositis severity is supported by head and neck cancer patients receiving concurrent chemoradiotherapy experiencing more severe mucositis than with radiotherapy alone (Trotti et al., 2003); the potential for TBI to result in either mucositis of greater intensity or earlier onset has not yet been demonstrated

2.4.2 Patient related factors

2.4.2.1 Previous history of mucositis

Previous occurrences of mucositis have been suggested as a factor in mucositis development (Kostler et al., 2001), due to damage sustained previously by cells below the mucosal surface making the patient more susceptible to subsequent bouts of mucositis (Cawley and Benson, 2005). However, this was not identified as a factor in mucositis development in any of the studies shown in Table 1, although it should be noted that only one study included a history of mucositis as a potential risk factor (Vokurka et al., 2009).

2.4.2.2 Age

The impact of age on the incidence and severity of mucositis is a contentious issue. It has been suggested that due to increased rates of cell division in this group, younger patients may be at a greater risk of mucositis (Pico et al., 1998, Sonis et al., 1978). Conversely, it has also been argued that due to a reduction in renal function associated with the aging process, older populations may be more at risk (McCarthy et al., 1998), due to reduced renal function increasing the toxicity of antineoplastic medications by altering their pharmacokinetic and pharmacodynamic effects (Avritscher et al., 2004). It is notable that while age was analysed as a potential risk factor by 12 studies, and was identified in the univariate analyses of three studies shown in Table 1 (Mattsson et al., 1991, Ohbayashi et al., 2008, Wardley et al., 2000), it was not identified in any of the

multivariate analyses, suggesting that age may not be an independent risk factor for mucositis development and may instead be associated with some other factor, such as type of disease or conditioning regime.

2.4.2.3 Smoking

Smoking was identified as a risk factor for mucositis development in only one study (Robien et al., 2004) shown in Table 1. However, this result is based on an extremely small subsample of only four patients. Conversely, smoking was not identified as a risk factor by McCarthy and colleagues (1998), the only other study which analysed this potential risk factor. Smoking cigarettes has been reported to significantly reduce the incidence of severe mucositis in patients in a study by Kazemian (2009), which investigated benzydamine for the prevention of mucositis. This analysis was again based on a small subset of 20 patients, and the results of this study do not appear to be supported elsewhere in the literature. More research into this area is warranted.

2.4.3 Summary of patient and treatment related factors

Table 1 shows the results of studies which have employed multivariate analyses in an attempt to identify treatment and patient related factors which may affect the development and severity of mucositis. There appears to be little consistency in the results of these studies, with only TBI and melphalan dose per kilogram of bodyweight being identified as possible factors by more than one study. More research is needed in this area is the prediction of at risk patients is to become a real possibility. However, stratification by whether or not a patient receives TBI should be considered in clinical trials conducted in patients undergoing transplantation. If such trials include both patients receiving high dose and low dose melphalan chemotherapy, then stratification by melphalan dose may be advisable.

2.5 Impact of mucositis

The impact of mucositis is threefold: its economic and clinical effects may be more obvious, but the impact of severe mucositis on the patient experience should not be overlooked. The next section of this literature review will discuss the impact of mucositis on each of these areas in detail.

2.5.1 Clinical impact of mucositis

2.5.1.1 Treatment breaks

Mucositis is a dose limiting toxicity (Peterson and Cariello, 2004) as severe mucositis can necessitate dose modifications or breaks in treatment to allow the patient to recover, which may adversely affect the outcome of treatment (Blijlevens et al., 2009, Epstein and Schubert, 2004, Scully et al., 2006). Indeed, very severe mucositis may force the complete cessation of treatment (Blijlevens et al., 2009).

2.5.1.2 Length of hospital stay

Several studies have reported that patients with severe mucositis require longer periods of hospitalisation compared to patients with mild or no mucositis (Sonis et al., 2001, Vera-Llonch et al., 2007a, Vera-Llonch et al., 2007b). Vera-Llonch and colleagues reported a five day difference in length of hospital stay between patients with severe mucositis and those with no mucositis ($P<0.001$) in a retrospective analysis of patients undergoing autologous transplantation (Vera-Llonch et al., 2007b). When allogeneic patients were studied using the same methods, length of hospital stay was longer still, with patients suffering from severe mucositis requiring a mean of 14 extra days in hospital compared to patients without oral symptoms ($P<0.0001$) (Vera-Llonch et al., 2007a). Two authors have used the oral mucositis assessment scale (OMAS) instrument to explore the clinical impact of mucositis (Bolwell et al., 2002, Sonis et al., 2001). Sonis and colleagues (2001), conducted a retrospective study of a mixed sample of 92 autologous and allogeneic patients undergoing stem cell transplantation and reported that a one-point increase in peak OMAS score was associated with an extra 2.6 days in hospital ($P<0.01$) (Sonis et al., 2001). While Bolwell and others (2002), prospectively studied 79 patients undergoing autologous transplantation using a modified version of the OMAS instrument, and reported that patients with a score of greater than one experienced a hospital stay six days longer than patients with a score of less than one ($P<0.001$) (Bolwell et al., 2002).

2.5.1.3 Pain

> "Pain is a clinically significant component of mucositis and an important factor on decreased quality of life among cancer patients" (Elting et al., 2003:1538)

Mucositis-induced pain is generally acute in nature and follows the pattern of mucositis development and resolution, reaching a peak approximately seven or eight days post-therapy and generally resolving by day 21 (McGuire et al., 1998). It is generally reported as being mild to moderate in intensity (Epstein and Schubert, 2004, McGuire et al., 1998). Like mucositis incidence, oral pain due to cancer treatment does not affect every patient in the same way. A small minority of patients will not experience oral pain at all. However, certain types of treatment are associated with higher incidence of pain due to mucositis than others. The incidence of oral pain is virtually 100% in the head and neck population (Alvarado et al., 2002, Epstein and Schubert, 2004). In the BMT population, reported occurrences of pain range between 47% and 86% (McGuire et al., 1993, Fall-Dickson et al., 2008). Among the general chemotherapy population, figures range between 40% and 70%, reflecting the incidences of mucositis in these populations (Alvarado et al., 2002). It has been suggested that the true incidence of mucositis related pain may be higher than that currently recognised in the literature (Epstein and Schubert, 2004), due to the under-reporting of the symptom by patients, or the under-recording or under-treatment of the condition by medical staff.

Head and neck cancer is commonly treated with surgery, radiotherapy or chemotherapy, or a combination thereof. Each of these treatment modalities is associated with pain (Epstein and Schubert, 2004). Surgery can result in acute pain, which may become chronic due to scarring or other musculoskeletal syndromes. Radiation can also cause acute pain, which continues to persist long after treatment has abated, and can cause long-lasting discomfort and sensitivity to the mucosa. The use of chemotherapy in conjunction with radiotherapy can intensify the level of mucosal damage, increasing the amount of pain experienced by the patient (Epstein and Schubert, 2004). Research has shown that pain control in this patient population is generally poor (Wong, 2006). Patients can therefore experience long-lasting pain due to treatment, which can have a significant impact both on clinical resources and patient quality of life.

Patients receiving the same types of treatment may not be expected to experience the same amount of pain, or interpret their pain in the same way. Indeed some patients have reported believing that their pain was a positive thing, as this meant that the treatment was working (Borbasi et al., 2002). A patient's perceived level of pain is multifactorial and is influenced by a number of physiologic, sensory, affective, cognitive, behavioural and sociocultural dimensions (Epstein and Schubert, 2004, McGuire et al., 1998). The physiological dimension of pain encompasses the cause of the pain, in this case mucositis, the duration and physical aspects of the pain (the ulceration and inflammation), and the temporal pattern of the pain: whether the pain is intermittent or chronic in nature (McGuire et al., 1998). The sensory dimension concerns what the pain feels like for the patient: its location and intensity (McGuire et al., 1998). The patient's emotional response to the pain, including, but not limited to, anxiety, depression and mood disturbances describes the affective dimension of pain (McGuire et al., 1998). The cognitive dimension refers to the patient's thoughts about the pain, the meanings attributed to the pain by the patient and any coping strategies employed. The patients attitudes in relation to pain, and the relief of pain, are also included in the cognitive dimension in this model (McGuire et al., 1998). The behavioural dimension of the pain model pertains to the patient's observable behaviours. Such behaviours can either be those attempting to alleviate pain, such as the use of painkillers, or alternatively, behaviours that indicate the presence of pain, such as grimacing (McGuire et al., 1998). The final dimension of pain is the sociocultural dimension of pain. This dimension covers the profusion of ethnic, spiritual, social, cultural, and demographic factors that influence a person's perception of pain and their response to this stimulus (McGuire et al., 1998). The patient's experience of pain is therefore very complex and is comprised of a number of inter-related factors, which affect both how the patient perceives their pain and how they deal with this pain. However, despite oral pain being identified as the most important symptom to be measured in clinical trials by both patients and Clinicians (Cella 2003), only 36% of the studies included in the 2010 update of the Cochrane review of interventions for the prevention of mucositis reported some type of pain measurement (Worthington et al., 2010).

2.5.1.4 Infection

Infection is possibly the most important complication of cancer treatment (Blijlevens et al., 2009, Brown and Wingard, 2004). The invasion of infective organisms into the

ulcerated mucosa also act to drive and amplify the fourth stage of the Sonis mucositis model (Sonis, 2009), through the production of positive feedback loops (Scully et al., 2006). Under normal conditions, the mucosal surface of the oral cavity acts as a barrier to prevent the passage of pathogens into the body. The shedding of the surface layer of the mucosa additionally acts to reduce the number of organisms colonising the oral cavity (Brown and Wingard, 2004). However, mucositis ulceration damages the integrity of this barrier and this allows the invasion of infecting organisms. Cancer patients who are suffering from neutropenia, the absence of neutrophils due to treatment, are considered most at risk of developing an infection. Patients undergoing transplantation, who commonly experience a prolonged period of neutropenia, have been shown to be three times more likely to develop streptococcal bacteraemia than patients without ulceration (Ruescher et al., 1998). The first, and sometimes only, sign of infection in neutropenic patients is generally a fever (Blijlevens et al., 2009). The occurrence of fever during neutropenia, a condition termed febrile neutropenia, is life threatening, and left untreated may result in the death of the patient due to sepsis (Blijlevens et al., 2009).

In their study validating the OMAS instrument, Sonis and others identified that a one point increase in peak OMAS score was associated with one additional day of fever, and just over twice the risk of significant infection ($P<0.01$ for both) (Sonis et al 2001). Prevention and treatment of infection has, through the need for increased use of prophylactic antibiotics and extra procedures and tests, a significant clinical impact. Such a clinical impact also has economic implications and can cause distress to the patient and their families.

2.5.2 Economic impact of mucositis

In addition to its clinically relevant impact, mucositis also exhibits a significant economic cost. More hospital admissions, and longer hospital stays, together with the administration of drugs to alleviate pain and fight infection, and interventions to prevent and treat the condition, result in higher costs for treating patients with, compared to patients without, mucositis. Various authors have attempted to quantify this economic impact, using a variety of methods. All these studies were conducted in the United States of America (USA), and therefore all figures given are in United States dollars ($).

Sonis and colleagues (2001), conducted an analysis of the economic impact of mucositis in BMT using data collected from 92 patients during the validation of the OMAS instrument. The authors obtained hospital charges for the 70 patients in the study based within the USA and calculated that a one-point increase in peak OMAS score was associated with additional hospital charges totalling $25,405 (Sonis et al., 2001). The authors also calculated that hospital charges were $43,000 higher, during the 100 days post-transplant, for patients who developed ulcerative mucositis compared with those who did not (Sonis et al., 2001).

In 2003, Elting and colleagues conducted a retrospective analysis of a cohort of 599 patients with solid cancers undergoing chemotherapy. The primary objective of this study was to study bleeding outcomes in these patients, and therefore the sample was comprised entirely of patients with neutropenia or thrombocytopenia. Hospital costs for this study were based on a daily fixed fee of $1000 per day, a figure derived from mean U.S medicare payments (Elting et al., 2003). The authors report that the occurrence of mucositis increased the cost of hospitalisation per cycle of chemotherapy by 62%, from $3893 per cycle in patients without mucositis to $6277 per cycle in patients with the condition (Elting et al., 2003). While the costs of mucositis in BMT patients reported by Sonis and colleagues (2001), were much higher than those reported by Elting and others (2003), the authors conclude that the number of patients treated with solid tumours is far greater than those receiving BMT, and therefore in aggregate, the costs associated with mucositis in this group may be greater than those associated with transplantation (Elting et al., 2003).

In 2007, Elting and colleagues published the results of a retrospective chart analysis of 204 head and neck patients who received treatment at the M.D. Anderson Cancer Centre during 2002, and calculated costs using data from the hospital's accounting system in 2002 and inflated to 2006 prices using the Consumer Price Index for Medical Care. The authors report that increased resource utilization due to mucositis resulted in costs escalating by $1700 in patients with mild mucositis (grades 1 and 2) and by $3600 in patients with severe ulcerative mucositis (grades 3 and 4) (Elting et al., 2007). The costs reported in this study varied considerably when subsamples of patients receiving

different types of treatment were analysed. In patients receiving radiotherapy only, the mean cost of treatment in patients without mucositis (after adjustment for patient and disease factors) was $14,646 (95% CI, $11,801 to $18,178) compared to $20,624 (95% CI, $19,227-$22,122) in patients with mucositis (P=0.006) (Elting et al., 2007). However, in patients receiving a combination of radiotherapy and chemotherapy, the difference in costs in patients suffering from mucositis compared to those without mucositis was not significant (P=0.35) (Elting et al., 2007).

All of the economic analyses of the costs associated with mucositis detailed in this literature review were conducted retrospectively. There are significant organisational challenges associated with attempting to conduct such analyses prospectively, which explains why no such study has been identified. However, this retrospective nature of data collection is problematic, as mucositis incidence may be underestimated, especially mild forms of the condition, which may bias the results of the study (Elting et al., 2003). Retrospective analyses are also at the mercy of the quality of oral assessment used at a centre. Peterman and colleagues (2001), conducted a retrospective chart analyses of 45 patients with head and neck cancer and reported that severe mucositis was associated with significantly higher costs for outpatient nutrition (P=0.03) and prescription medications (P=0.0005). However, the authors concluded that variability in the use of a single method of oral assessment by different assessors, and the failure of assessors to employ a single grading system may have introduced unmeasured error into the results (Peterman et al., 2001). The results of this study are therefore highly questionable.

To date, no attempt has been made to quantify the economic impact of mucositis in British patients. The structure of healthcare in the United States, with its methods of direct billing, lends itself to such economic evaluations, and it would be difficult to replicate such studies using the British publicly funded healthcare model. Likewise, care should be used when applying these American-generated costs in Britain, due to the differences in our health systems. However, even without such direct figures it can be concluded that mucositis has a significant economic impact.

2.5.3 Impact of mucositis on the patient experience

Patients' reports of mucositis can be separated into two groups: those collected quantitatively using questionnaires; and those made during qualitative interviews. To date, four qualitative studies have been conducted to study mucositis from the patient's perspective.

Borbasi and colleagues, (2002) qualitatively interviewed six patients undergoing autologous transplantation. The four male and two female patients, aged between 38 and 63 years old, were interviewed weekly during hospitalisation for four weeks and then at eight weeks and 12 weeks post transplant. In total, 19 out of a planned 36 interviews were conducted. Although it was anticipated that interviews would last between 45 minutes and one hour, some interviews were shorter, and three patients refused to be interviewed when their mucositis was at its most severe (Borbasi et al., 2002). Three patients died during data collection, and an unspecified number of patients had to be interviewed over the telephone post-discharge, due to problems keeping hospital appointments, indicating how difficult it is to conduct research in this area. Patients were asked to relate their symptom experience of mucositis at various stages of the transplant process to an interviewer and to keep a record of thoughts and feelings in a diary. Unfortunately, such diaries were underutilised, probably due to the severity of illness experienced by this group (Borbasi et al., 2002).

Using a phenomenological analysis, the authors identified three phases of the transplant process: the preparatory, peak and persisting phases; and five key themes: 'the presence of nurses', 'therapeutic interventions', 'manifestations of mucositis', 'the distress of eating (and not eating)' and 'whether the treatment was worthwhile' (Borbasi et al., 2002, p1051). Although the patients encountered different severities of mucositis, all experienced some symptoms, with patients describing 'tingling' and mild sore throat at the onset of mucositis. As mucositis increased in severity, taste changes and difficulty with chewing and swallowing, loss of appetite, xerostomia and pain were reported. All patients experienced periods of low mood due to their symptoms, with some describing feelings of social isolation due to the discomfort associated with the condition (Borbasi et al., 2002). In addition to reporting an increase in feelings of anxiety at mealtimes, due to problems swallowing, patients also reported frustration that their symptoms made the

prospect of eating unappealing. Patients also reported periods where they were unable to eat, which they found distressing as they associated the ability to eat with recovery (Borbasi, 2002).

Two patients continued to experience mucositis symptoms post-discharge. One patient reported swallowing problems at five weeks post-treatment. These problems continued to persist and were still negatively impacting his quality of life 11 weeks after transplantation. Another patient reported the use of artificial saliva at six weeks post-transplant, and stated that her eating and drinking related were worse at this time than they had been during treatment (Borbasi et al., 2002).

Although the authors experienced many problems collecting data, the results of this study are important as they suggest that in addition to causing pain and problems eating, severe mucositis can increase patients' feelings of anxiety, distress and social isolation, impairing their quality of life. Interestingly, the authors comment that, although patients believed that they had been prepared for mucositis symptoms, in reality they were actually only prepared for the physical manifestations of mucositis, and not the psychological aspects of the condition (Borbasi et al., 2002). How exactly therefore, do we prepare patients for the psychological onslaught of mucositis? Unfortunately this question has not been addressed in the literature to date.

To date, the Borbasi and colleagues study is the only prospective qualitative study conducted to explore patient reports of mucositis. The problems conducting interviews with patients while mucositis was at its peak, and the level of attrition experienced, illustrate the problems of conducting research in the transplant population. Three retrospective qualitative studies have been published. All of these studies will be susceptible to recall bias. Cheng (2009) conducted the only qualitative study to date exploring reports of mucositis in children. This phenomenological study aimed to describe the lived experiences of mucositis. Semi-structured interviews were conducted with 22 paediatric patients who had experienced ulcerative mucositis within six months of interview and their parents. The mean age of children taking part in this study was 12.1 years old; the youngest patient recruited was six, and the oldest was 19 years old

(Cheng, 2009). Twelve of the children recruited were male. Nine patients had a diagnosis of acute lymphoblastic leukaemia, seven had osteosarcoma and four patients suffered from lymphoma. The diagnosis of the remaining two patients was unspecified (Cheng, 2009). The vast majority of the parents recruited were female (91%). One male parent and one grandmother also took part in the interviews (Cheng, 2009). The interviews conducted with children lasted between 20 and 30 minutes, although the author states that the youngest children often took part in shorter interviews.

Like Borbasi and colleagues, Cheng (2009) identified five themes: 'symptoms experienced', 'negative emotional outcomes', 'the dilemma of eating (or not eating)', 'challenges in oral care' and 'healthcare needs' (Cheng, 2009, p831), and fourteen categories: 'consequences of pain', 'location of ulceration', 'control of pain', 'distress of children', 'emotional tension', 'distress of parents', 'eating is fundamental to life', 'poor nutritional status' and 'weight loss', 'importance of oral care', 'pressure to do mouthcare', 'children's co-operation', 'education needs', 'psychological preparation' and 'compassionate care'(Cheng, 2009, p831).

The patients interviewed by Cheng experienced a great deal of pain, which was present despite the administration of opioids. This pain was described as the worst aspect of oral mucositis by the children. Oral mucositis led to social isolation for some patients as they were unable to speak due to their symptoms (Cheng, 2009). When interviewed, parents specified the need for better education about mucositis, in order to make them better prepared to deal with the condition psychologically (Cheng, 2009). Both patients and parents felt that they were underprepared for the severity of mucositis and its associated symptoms, and suggested a need for psychological support, and organised displacement activities for patients, to help both groups deal with the situation (Cheng, 2009).

Cheng found that eating, or the lack of it, caused distress to both patients and their carers (Cheng, 2009). Like the patients interviewed by Borbasi and others, the parents interviewed by Cheng equated eating with recovery and survival, and experienced conflicting emotions encouraging their child to eat because of the suffering that eating caused (Cheng, 2009). Both patients and carers also described mouth care as a source of

conflict and distress, as while children were aware of the importance of a clean mouth, the unpleasantness of the mouthwashes and the pain and discomfort involved in this process, led to oral care being neglected unless the child was encouraged or 'forced' by a parent (Cheng, 2009). Unfortunately, a major criticism of Cheng's results is that the author does not state how old the patient is in the quotes provided, and does not discuss if there were any potential differences in the symptoms reported in different age-groups of children.

Bellm and colleagues (2000) conducted qualitative interviews with patients who had undergone transplantation within the previous 18 months at marketing research facilities in five cities in America. Patients were recruited through support groups, physician and patient referral, and adverts placed in newspapers. All patients received honoraria of an unspecified nature for taking part in the study. Of the 38 patients recruited, ten were male and 28 were female. The mean age of subjects was 46.9 years old (Bellm et al., 2000). When asked to recall the most debilitating aspect of their treatment, 42% of patients stated that mouth sores were the most incapacitating. The next most frequent side effect recalled by patients was nausea and vomiting (13%). Of the patients reporting mouth sores as a side effect of treatment, 23 patients reported difficulties in eating, 21 reported a restriction in swallowing, 17 patients reported difficulties drinking and eight problems with talking (Bellm et al., 2000).

The authors state that these interviews were 'in depth' however, according to the interview key, the entire interview only lasted approximately 50 minutes, with 17-20 minutes of this time being taken up with product testing of three oral mucositis products. After time for introductions and questions about the transplant experience, it is surmised that this leaves approximately ten minutes for oral mucositis questions. It is therefore doubtful if the interviews where of a long enough duration to be considered to be 'in depth'.

The results of the Bellm and colleagues study are also at risk of recall bias, as while the authors intended to recruit patients who had undergone transplant in the previous 18 months, only 60% of the sample met this criteria, with another 24% of patients having

had a transplant between 18 and 24 months before interview and the remaining 16% having had a transplant between three and six years before interview (Bellm et al., 2000). Furthermore, the authors used a qualitative methodology to collect data and then chose to describe their finding quantitatively. While this method provides some interesting mucositis statistics, it seems that the chance to produce a richer narrative about the patient experience of mucositis has been missed.

Rose-Ped and colleagues (2000) conducted a similar study with patients undergoing radiotherapy for head and neck cancers in 2002. The patients were recruited and interviewed using the same methods as Bellm and colleagues (Bellm et al., 2000). A total of 33 patients were recruited, of which 61% were male. The mean age of patients recruited into the study was 56.4 years old (Rose-Ped et al., 2002). To be eligible to take part in this study, patients originally had to have completed radiotherapy between January 1997 and October 1998; however, patients who completed radiotherapy before 1997 were also included due to problems with recruitment, with five patients who received radiotherapy during or before 1995 being included in the sample, making the possibility of recall bias a possibility once again. The interviews were longer than in the previous study, with patient dialogues lasting approximately 45 minutes.

When asked to describe the most troubling side effects they experienced during treatment, patients reported sore throat (20%), mouth sores and pain (18%), and xerostomia (14%) most frequently. Eighty-eight percent of the patients interviewed reported that mucositis impaired their ability to eat and drink, resulting in weight losses in 83% of patients which ranged from 12 pounds (5.44kg) to 79 pounds (35kg). Patients' reports of time to mucositis development and resolution varied considerably, with mucositis developing on average within 2.5 weeks after the start of radiotherapy, with a range of one to eight weeks. Time taken to resolution ranged from two to 24 weeks, with a mean time to resolution of 8.7 weeks (Rose-Ped et al., 2002). Ninety percent of patients reported taste changes, with 54% of patients reporting that they experienced a complete loss of taste (Rose-Ped et al., 2002). Unfortunately, once again the authors miss the opportunity to provide a rich narrative of the mucositis experience, instead favouring the quantitative reporting of findings.

Stiff (2001) reports the results of a 'retrospective survey' of 41 patients who underwent BMT at his institution, 30 of whom received autologous transplantation. Of the patients interviewed, 50% reported mucositis as the most debilitating side effect associated with their treatment, followed by nausea and vomiting (29%), diarrhoea (8%) and rash (3%) (Stiff, 2001). These data seem to support the figures reported in the Bellm and colleagues study (Bellm et al., 2000), with the slight disparity between the reports probably due to Bellm and colleagues asking patients specifically about mouth sores while Stiff appears to have asked about mucositis.

Using the Loyola BMT toxicity scale, Stiff reports that 29% of patients rated their mucositis as 'ten out of ten' (worst possible), compared to 12% of the sample reporting 'five out of ten'. The average reported level was nine (Stiff, 2001). No patients reported severity of mucositis below level five. One very interesting element of this retrospective survey is that mucositis was more severe than expected in 84% of patients surveyed (Stiff, 2001). In addition, 65% of patients interviewed reported that they received no interventions to control their symptoms, or alternatively, that when such interventions were used, they were inadequate, resulting in only a 50% improvement in symptoms (Stiff, 2001). Of the patients reporting mucositis as the worst toxicity they experienced during transplantation, 65% (n=13) of patients reported that they were still experiencing residual symptoms when contacted to take part in the survey, while 50% of patients (n=7) experiencing reporting that they were experiencing xerostomia (Stiff, 2001). These residual symptoms reported by Stiff support data collected during quantitative interview by Borbasi and colleagues (Borbasi et al., 2002), and suggest that patients continue to suffer from oral complications long after the visual signs of mucositis (ulceration) have resolved.

While the results reported by Stiff (2001), are very interesting and appear to support the work of others, this report is not without criticism. These data were not published independently, and instead included as part of a much larger review of mucositis during stem cell transplantation. As this was only a short report, only basic patient characteristics are given, which do not extend to the age, gender or disease status of the patients surveyed, nor anything but the most basic details of the method of interviewing them. The author states that 25 patients had undergone transplantation in excess of a

year prior to completing the survey, while 11 patients had been transplanted during the six months before the survey (Stiff, 2001). Presumably, therefore the five outstanding patients had received a transplant between six months and a year prior to the survey. Unfortunately, when discussing the patients still reporting latent oral effects at the time of survey, the author does not state when these patients were transplanted, which limits the usefulness of this information, as it is not possible to determine how long patients were continuing to experience oral symptoms post-transplantation.

Patient reporting of mucositis is an under-researched area. While there are hundreds of studies of interventions for the prevention, treatment and management of mucositis, the literature surrounding the patient experience of mucositis is scarce. To date, only four qualitative studies have interviewed patients about their experiences of mucositis, and only one of these studies has been conducted prospectively. Many of the patients interviewed described pain as the worst symptom of mucositis (Cheng, 2009), however, of the 89 studies included in the 2007 update of the Cochrane review of interventions for mucositis prevention, only 26 studies directly measured patient reports of pain, or collected data on use of analgesia as a proxy measure of pain levels (Worthington et al., 2007). In addition, only three studies measured patient ability to eat or drink (Worthington et al., 2007), suggesting that the focus of research is the physical signs of mucositis (ulceration) rather than the symptoms that patients report as most the distressing elements of the condition. Patients from a number of studies describe their mucositis as being worse than they had previously expected, and that some of these symptoms continued to impact their quality of life after the ulceration had resolved. It is clear from the small amount of data available that patients and their families have a number of unmet needs that are still to be addressed.

2.6 Conclusion

Oral mucositis is a distressing treatment-related toxicity which exerts both a clinical and economic impact and negatively affects patient quality of life. Incidences of mucositis as high as 75 to 100% have been reported in bone marrow transplant patients. Severe mucositis extends the length of hospital stay, increases a patient's susceptibility to infection and demand for opiate pain relief and can necessitate breaks in treatment, which in turn can adversely affect treatment outcome. Patient experiences of mucositis

are underreported in the literature. Significant gains could be made if such a disease could be prevented, especially within high risk patient groups such as patients undergoing transplantation. The ability to effectively prevent mucositis would arguably be more advantageous than the capability to treat the condition, as effective prevention would be of economic and clinical benefit, and positively impact patient quality of life. Based on the need for interventions to prevent oral mucositis in patients with cancer undergoing therapy established by this literature review, the next chapter will consider published reports of interventions trialled for the prevention of mucositis.

Chapter 3 Prevention of Mucositis

3.1 Introduction

The prevention of oral mucositis has been identified as being advantageous in the previous chapter. This chapter will focus on the use systematic reviews to detail the results of interventions previously trialled for the prevention of mucositis.

3.2 Randomised Controlled Trials

A variety of different interventions have been studied for the prevention of oral mucositis. A large number of these studies have been conducted as randomised controlled trials (RCTs). In an RCT, participants are randomized to either the experimental arm, in which they are to receive the intervention under investigation, or the control arm, where they receive a placebo, no treatment or an alternative treatment. At the end of the study these groups are compared and the pre-specified outcomes measured to determine if the intervention is better than the other treatment or control (Jadad 1998). RCTs have been called the ‘gold standard’ method of conducting research that assesses the effectiveness of interventions, however this moniker is a matter of debate (Grossman and Mackenzie, 2005).

As the results of large numbers of RCTs are published each year, it is difficult for an individual, such a Clinician, researcher or patient, to read each one of these reports and decide on their own if a particular intervention is effective for a condition or disease overall. Therefore the results of RCTs are often discussed in reviews. The combination of study results can strengthen the evidence for the effectiveness, or ineffectiveness, of a particular intervention, or alternatively show that it is ineffective.

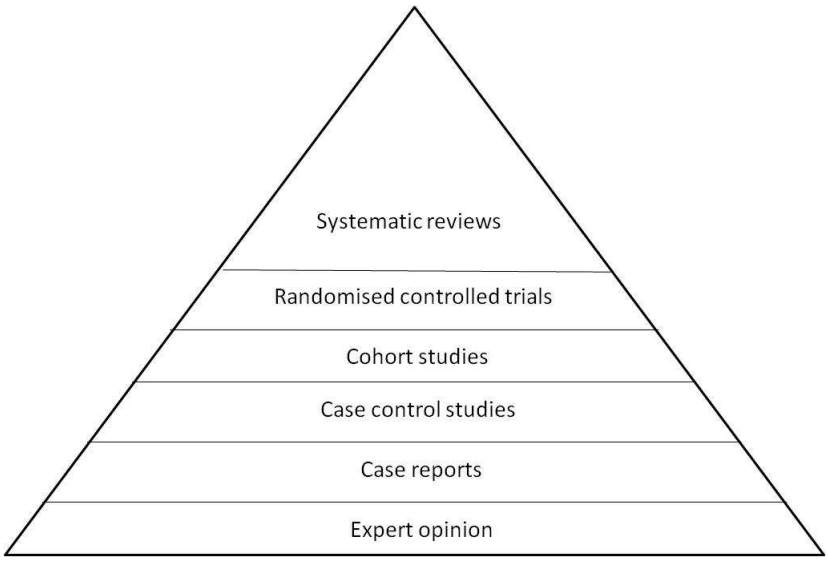


Figure 4: Hierarchy of Study Evidence

(adapted from Mantzoukas, 2008)

There are two broad types of reviews: traditional literature reviews and systematic reviews. Traditional reviews have been described as haphazard and biased, often reflecting the opinion of the review's authors (Mulrow, 1987). Systematic reviews, however, aim to provide a more objective, comprehensive overview of the research literature in order to obtain a reliable summary that may assist in the clinical decision making process. Systematic reviews follow explicit, well-documented, scientific methodology in order to reduce both systematic errors (biases) and random errors (those occurring by chance). The combining of studies within a systematic review may include a meta-analysis, providing a more powerful estimate of effect, although this is not always appropriate. Meta-analysis is the statistical pooling of data from two or more studies (although it is sometimes used to refer to the whole review process). Systematic reviews of RCTs occupy the top tier of the hierarchy of study evidence pyramid shown in Figure 4.

3.3 Systematic Reviews

General reviews of the literature provide an overview of the subject, usually in the form of a description, with little critical analysis (Bowling, 2002). These studies do not generally supply information about how a literature search was conducted, how the information was chosen for inclusion or how decisions were made about the exclusion of some of the literature. Selection bias is therefore a potential problem with these

reviews, as the author may have purposely chosen not to include a study because the data contradicts the previous work or author opinion. Systematic reviews avoid these issues by having an explicit search strategy and inclusion criteria before any literature searching takes place. An assessment of trial quality is also usually conducted. In a meta-analysis, the data from trials identified in a search may be pooled and analysed to produce a single result from the aggregated data (Bowling, 2002). This pooling of data controls for sample size and site specific effects and strengthens the power to detect true effects (Bowling, 2002). The Cochrane Collaboration is an independent organisation which produces a vast array of systematic reviews and meta-analyses on a variety of topics. The Collaboration was founded in 1993 with the aim of providing accurate information about the effects of healthcare interventions to the world.

3.4 Cochrane review for the prevention of mucositis in patients receiving treatment for cancer

A systematic review of interventions for the prevention of oral mucositis was first published by the Cochrane Collaboration in 2000 and has been constantly updated (Clarkson et al., 2000, Clarkson et al., 2003, Worthington and Clarkson, 2002, Worthington et al., 2006, Worthington et al., 2007). The latest update of the review is due to be published in December 2010. The Cochrane prevention review only includes studies which provide mucositis data on a zero to four point scale, such as the WHO or CTCAE instruments (Cancer Therapy Evaluation Program, 2009, World Health Organization (WHO), 1979). These data are dichotomised as follows: any mucositis, moderate plus severe mucositis, and severe mucositis (Worthington et al., 2007). In the 2007 update of the review, 277 studies were eligible but only 89 studies were included. The majority of the 188 excluded studies were ineligible because data were not in the correct format with mucositis data presented in the form of number of days with mucositis or as an area under the curve analysis. The 2010 update of the review, 379 studies were eligible for inclusion into the review, of which 248 were excluded for a variety of reasons. One-hundred-and-thirty studies were included, of which 13 were text only inclusions. In total 43 interventions were included in the review: acyclovir, allopurinol mouth rinse, amifostine, antibiotic pastille or paste, benzydamine, beta carotene, chamomile, chewing gum, Chinese herbs (two different types), chlorhexidine, clarithromycin, cryotherapy, dental stent, epidermal growth factor, glutamine, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-

stimulating factor (GM-CSF), histamine gel, honey, hydrolytic enzymes (two different types), indigowood root, intestinal trefoil factor, iseganan, keratinocyte growth factor (GF), laser, oral care, pentoxifylline, pilocarpine, polaprezinc, povidone-iodine, prednisone, propantheline anticholinergic, prostaglandin, morning versus evening administration of radiotherapy, shenqi-fanghou, superoxide dismutase (SOD), sucralfate, traumeel *S*, yangyin-humo decoction and zinc sulphate. However, only 18 of these interventions were included in the meta-analysis, as the remaining interventions either provided data from only one study (and were therefore included in the single studies table), or presented data for more than one study, but in different dichotomies. In addition, hydrolytic enzymes and Chinese herbs were separated into single studies and placed in the single studies table because the included studies had significantly different drug compositions, which prohibited pooling of these data.

3.4.1 Mugard and Caphosol

Two interventions were notable in their absence from the review: Mugard and Caphosol (a calcium phosphate rinse) are both oral rinses currently vigorously promoted for the prevention and treatment of mucositis in the United Kingdom. However, the evidence for the efficacy of either intervention is scant. To date, no prospective trials of Mugard have been published, and all manufacturer claims of efficacy are based on the results of studies employing a historical control group, data from one of which are discussed on their website but with no academic references provided (Access Pharmaceuticals INC, 2009). There are concerns about the underreporting of mucositis in such datasets, especially those in which mucositis incidence is not the main focus of investigation, and instead is recorded as an adverse event, which may be the case in trials which investigated the efficacy of a particular cancer treatment (Sonis, 2010). Although one randomised double blind study of Caphosol has been conducted, this study was excluded from the prevention review due to confounding as, in addition to Caphosol rinse, the intervention group received fluoride oral dental trays, while the control group received saline trays (Papas et al., 2003). The two other studies referenced by the manufacturer in its publicity material employ historical control groups. This lack of proven efficacy is concerning, as the manufacturers of Caphosol, Eusa Pharma, currently run a patient information website called “mouths made good” which in addition to providing general mucositis information, heavily advertises the product.

Well designed and conducted, prospective, double blind RCTs are required to test the claims made by the manufacturer regarding the potential for mucositis prevention with these products.

In the Cochrane prevention review, nine interventions were found to be beneficial for the prevention of mucositis in comparison to either a control or placebo in at least one dichotomy: aloe vera, amifostine, antibiotic pastille or paste, cryotherapy, glutamine, honey, keratinocyte growth factor (keratinocyte GF) and laser. However, only three interventions, cryotherapy, honey, and keratinocyte GF, were found to be statistically significantly better for the prevention of mucositis at all three dichotomies of interest (any versus none, moderate plus severe versus any and none, and severe versus moderate plus severe, any and none). This is a notable result, as cryotherapy and honey are 'low-tech' and relatively cheap interventions; while in comparison keratinocyte GF is expensive.

3.4.2 Keratinocyte GF

Keratinocyte GF, otherwise known as Kepivance (palifermin) or Repifermin, is a fibroblast growth factor which stimulates cell proliferation and differentiation resulting in epithelial tissue thickening (Blazar et al., 2006, Brizel et al., 2008). This increase in cell proliferation counteracts the destruction of the mucosal layer during the administration of cancer therapy. Data from six trials were entered into the prevention review meta-analysis: two studies were conducted in patients receiving chemotherapy for colorectal cancers (Meropol et al., 2003, Rosen et al., 2006), one study was conducted in patients receiving chemoradiotherapy for head and neck cancer (Brizel et al., 2008). The remaining three studies were conducted in patients undergoing stem cell transplantation: two were conducted in autologous patients receiving either chemotherapy and TBI or a mix of regimes (Freytes et al., 2004, Spielberger et al., 2004), and one was in patients receiving allogeneic transplantation (Blazar et al., 2006). Five of the six studies employed a form of growth factor named Kepivance (Palifermin) (Blazar et al., 2006, Brizel et al., 2008, Meropol et al., 2003, Rosen et al., 2006, Spielberger et al., 2004). The remaining study used Repifermin compared to placebo in

a phase one/two trial design (Freytes et al., 2004). In total, 598 patients were studied in the six studies.

Keratinocyte GF was found to be beneficial for the prevention of OM at all three levels of interest. However, a considerable amount of heterogeneity was identified in meta-analyses for the prevention of any mucositis (Chi^2=10.11, df=1 (P=0.001), I^2=90%) and moderate plus severe mucositis (Chi^2= 32.92, df= 5 (P<0.0001), I^2=85%). After exploration, this heterogeneity was hypothesised to be a result of the large amount of variation in the dose and scheduling of Keratinocyte GF, and differences between the patient groups in terms of cancer type and method of treatment (Worthington et al., 2010). This heterogeneity could indicate that keratinocyte is beneficial for mucositis prevention across a broad range of treatment and patient factors. This intervention however is not without its drawbacks. It is very expensive, costing £544.24 per vial (Anonymous, 2010); and as the typical regimen for transplantation involves three doses of keratinocyte GF before conditioning therapy and three days after the administration of stem cells (Spielberger et al., 2004), the total cost per patient for a course of treatment is £3265.44 (Anonymous, 2010), which may prohibit its use in certain countries, especially those in which a patient's level of health insurance cover may affect treatment choices. Palifermin is a Keratinocyte GF which has also been associated with a number of adverse events. Very common events, which represent more than 10% of all events include: taste alterations, thickening of the lining of the mouth and discolouration of the oral cavity, peripheral oedema, rash, pruritus, joint pain, erythema and fever (European Medicines Agency, 2010).

As well as the expense and number of adverse events associated with Keratinocyte GF, concerns have been raised about the suitability of the use of growth factors in children, as the long term safety of the drug and its potential impact on secondary malignancies is not known (Electronic Medicines Compendium, 2010). The safety profile of this drug when used concomitantly with therapy for non-haematological malignancies is also unproven (Electronic Medicines Compendium, 2010). In addition, the Medicines and Healthcare products Regulatory Agency (MHRA) recently restricted the use of Kepivance to only autologous patients undergoing conditioning with both chemotherapy and TBI (MHRA, 2010). This change was due to the results of a, to date unpublished,

double blind RCT conducted in patients with multiple myeloma undergoing autologous transplantation, which showed no therapeutic benefit in the reduction of severe mucositis duration or frequency in favour of palifermin, and suggested that patients treated with palifermin experienced more serious adverse events and treatment related adverse events than patients in the placebo group. These results changed the risk-benefit analysis for the use of the drug to such an extent that the MHRA and the European Medicines Agency have both issued updates to Healthcare professionals warning against its use in autologous patients receiving therapy with chemotherapy alone (MHRA, 2010). Whilst Keratinocyte GF appears to be beneficial in the prevention of mucositis, its expense, association with adverse events and the restrictions on its use, mean that keratinocyte GF is not a suitable agent for the prevention of mucositis in most patient populations.

3.4.3 Cryotherapy

Cryotherapy, the application of crushed ice or ice pops during chemotherapy, was another intervention found to be beneficial at all dichotomies of interest. Six studies provided data for this intervention, one of which was a text only inclusion as the data were not in the correct format for inclusion into the meta-analysis. This study was a parallel group study of 18 patients undergoing conditioning for allogeneic BMT (Svanberg et al., 2007). Of the remaining five studies, three were conducted in patients receiving chemotherapy with 5-fluorouracil (5-FU) in combination with other drugs (Cascinu et al., 1994, Mahood et al., 1991, Rocke et al., 1993), while the remaining two studies were conducted in patients undergoing stem cell transplantation (Gori et al., 2007, Lilleby et al., 2006). None of these studies employed any form of patient or outcome assessor blinding. In total data from 527 patients were included in the meta-analysis. Once again statistically significant heterogeneity was identified for the outcome any mucositis (chi square 14.77, df=4, P=0.005, I^2=73%), moderate plus severe mucositis (chi square = 19.02, df=4, P=0.0008, I2=79%), and severe (chi square 14.31, df=4, P=0.006, I^2=72%). Cryotherapy is hypothesised to prevent mucositis through a decrease in blood flow to the oral cavity as a consequence of vasoconstriction, leading to the mucosal receiving less exposure to chemotherapy (Lilleby et al., 2006). This intervention is therefore potentially most beneficial in chemotherapy drugs which have short-half lives, such as 5-FU. However, it is currently unclear if cryotherapy may

be of benefit either in the prevention of mucositis induced by radiotherapy or in the prevention of mucositis induced by chemotherapy drugs with longer half lives.

3.4.4 Honey

Honey was the final intervention which was found to be beneficial at all three dichotomies of interest. Data from three studies were entered into the meta-analysis, two of these studies were conducted in patients receiving radiotherapy for head and neck cancer (Biswal, 2003, Rashad et al., 2008), while the remaining study was performed in patients receiving radiotherapy for head and neck cancers (Motallebnejad et al., 2008). In total data from 120 patients were entered into the meta-analysis, as all studies each recruited 40 patients. Only one study employed outcome assessor blinding (Motallebnejad et al., 2008). The application of honey is hypothesised to speed up wound healing through epithelisation (Biswal, 2003). Honey also has antimicrobial properties (Rashad et al., 2008). Patients in these studies were asked to move the honey around their mouth in order to coat the mucosa, before swallowing it. However, this may be difficult for patients suffering from xerostomia (absence of saliva), or trismus (constriction of the mouth), both of which are common side effects of radiotherapy.

The submitted update of the Cochrane prevention review, to be published in November 2010, has highlighted three potential interventions for the prevention of mucositis. However, none of these interventions have been found to be universally beneficial for the prevention of mucositis for all types of cancer therapy, and all three interventions have potential drawbacks either in terms of the intervention itself, or the available evidence. The cost of a course of therapy and the scale of the side effects associated with its use are disadvantages of keratinocyte GF application. The lack of outcome assessor blinding in all cryotherapy trials, and all but one of the honey studies, and the small numbers of patients entered into the honey studies are also matters of concern. Whilst the 2010 version of the prevention review has made gains in the synthesis of information about interventions that are, and are not, beneficial for the prevention of mucositis, a ‘golden bullet’ intervention to solve the problem has still not been identified. Further clinical trials are therefore crucial.

3.5 Potential weakness of the review

The exclusion of studies employing multi-component instruments is arguably the greatest weakness of the Cochrane prevention review, as the variety of different mucositis assessment instruments available results in large numbers of studies being excluded. However, it would be very difficult, if not impossible, to find a method of including data from all available studies, due to the number of ways that data are presented. Therefore, the inclusion of studies that present data that can be dichotomised in the manner above currently constitutes the best method of producing meaningful results. In an attempt to counter this weakness, the text from a number of studies which included data which were not in the correct format, but which employed an appropriately subjective assessment instrument were included in the 2010 update of the review as additional information. However, this has not prevented whole interventions from being excluded from the analysis. One such intervention is vitamin E. Two studies have been conducted investigating vitamin E in the prevention of vitamin E (Sung et al., 2007, Ferreira et al., 2004). One of these studies was excluded because the data presented were in the wrong format (Ferreira et al., 2004), while the other was an 'n-of-1 study' (Sung et al., 2007), in which each patient served as their own control, a method of analysis which cannot be presently incorporated into the meta-analysis. Neither of these interventions could be included as text only inclusions in the review due to one of these studies presenting data in the form of weeks of mucositis and the other study employing data in a format which were not compatible with other studies.

3.6 Justification for the choice of vitamin E as the intervention for the feasibility study

The Cochrane prevention review was used as the basis for deciding on an appropriate intervention. A list of interventions which had either been identified as requiring more research; or which had been excluded from the review due to data being in an inappropriate format, was drawn up by the author, who then considered the possibility of running a small non-commercial feasibility trial using these interventions, with a limited budget and within a three year timescale. It was apparent that a number of interventions were not appropriate as these were produced under licence by pharmaceutical companies, which were unlikely to allow a novice researcher the use of their product for a clinical trial. Honey was briefly considered as a possible intervention, however, as a similar trial was being conducted at the proposed study site this was discounted as a possible intervention. After careful consideration vitamin E was

eventually chosen because: 1) while it appeared beneficial for the treatment of mucositis, there was conflicting information on whether this intervention was beneficial for the prevention of mucositis; 2) previous trials had been assessed as being at unclear risk of bias and there was a need for a well-designed, conducted and reported trial using this intervention, 3) it was easy obtainable and relatively cheap, which meant that such a trial could be conducted using a small budget and 4) vitamin E had been previously studied in patients undergoing both chemotherapy without any identified effect on chemotherapy efficacy.

3.7 Vitamin E

Vitamin E is a fat soluble vitamin that exhibits anti-oxidant and anti-inflammatory effects, preventing the peroxidation of the polyunsaturated lipids in membranes (Olson, 2000). The predominant source of the vitamin in the diet are oils derived from plant products (Zingg, 2007). D-α-tocopherol (RRR-alpha-tocopherol) is the most active form of the vitamin (Gonzalez, 1990). Other forms of alpha-tocopherol are shown in Table 2.

Table 2: Forms of Alpha Tocopherol.

	International units (iu)/ mg	Relative activity
D-alpha-tocopherol	1.49	1.00
D-alpha tocopherol acetate	1.36	0.91
Dl-alpha-tocopherol	1.10	0.74
Dl-alpha-tocopherol acetate	1.00	0.67

(Adapted from Bender, 2005)

3.7.1 Vitamin E for the prevention of mucositis

Ferreira and colleagues (2004) studied vitamin E in the prevention of radiation-induced mucositis in patients with head and neck cancers. In this study 45 patients were randomised to receive vitamin E, 800mg (as 400mg twice a day), or control, 500mg/mL of evening primrose oil. Immediately before radiation therapy, patients were asked to dissolve the capsule in saliva and rinsed their mouth with the solution for five minutes, before swallowing. The procedure was repeated between eight and 12 hours later for the second dose of vitamin E or placebo. Patients were followed from the beginning to the end of their radiation treatment. A difference in the number of mucositis events observed was reported, with the intervention group experiencing 17 fewer events than the control group ($p=0.038$). The authors also reported a significant difference in pain scores for patients in the intervention group ($p=0.0001$) (Ferreira et al., 2004).

Sung and colleagues (2007) performed a series of double blind N-of-1 trials using vitamin E for the prophylaxis of chemotherapy-induced oral mucositis in paediatric chemotherapy patients. The authors enrolled 16 patients, with median age of 12.7 years, scheduled to receive doxorubicin chemotherapy. Ten of the children in this study were male (Sung et al., 2007), and nine had a diagnosis of Ewing's Sarcoma, three had a diagnosis of large cell lymphoma, three had a diagnosis of osteosarcoma and one patient relapsed embryonal rhabdomyosarcoma. Forty-five post chemotherapy cycles were randomised with patients allocated to receive either 800mg of vitamin E or a corn oil placebo. Vitamin E was administered diluted in corn oil, and the patients were asked to expectorate the solution after rinsing. Six patients failed to complete the study, three of whom withdrew due to premature discontinuation of doxorubicin. The authors report that patients receiving vitamin E experienced a lower mean mucositis score per cycle of chemotherapy than patients in the placebo group (0.2 in the vitamin E arm compared to 0.3 in the placebo arm). However, this difference was not found to be statistically significant (Sung et al., 2007).

3.7.2 Vitamin E for the treatment of mucositis

Two studies have also shown positive effects in the treatment of oral mucositis. Wadleigh and colleagues (1992) conducted the first trial of vitamin E in the treatment of chemotherapy-induced mucositis. In this single blind study, patients were randomised to receive either a topical application of vitamin E, or a placebo, consisting of a mixture of coconut and soyabean oil. These were administered upon the appearance of oral lesions, in a dose of 800mg (as 400mg twice a day). In total, 18 patients were randomised to take part in the study, 11 of these patients were being treated for head and neck cancer, five for oesophageal cancer, one patient for acute myelogenous leukaemia and one for hepatoma. In patients randomised to the intervention group, 66% experienced resolution of mucosal symptoms within four days, while, 88% of the control group did not experience resolution of symptoms during the study period ($p=0.025$) (Wadleigh et al., 1992). The results reported are impressive; however, the methodology suffers from a small sample size ($n=18$), and a short follow-up of five days.

El-Housseiny and colleagues (2007) also studied paediatric cancer patients. The authors recruited 80 patients with chemotherapy-induced oral mucositis and randomized them to receive either 100mg of topical vitamin E or 100mg systemic vitamin E twice daily. No control group was employed. Both groups were followed for five days. 63 patients completed the follow-up period and were included in the final analysis. At the end of the trial, in the group of patients who received vitamin E topically 24 patients (80%) experienced fully resolution of their symptoms, two patients (6.7%) had world health organisation (WHO) grade one mucositis, two patients (6.7%) had WHO grade two mucositis and one patient had grade four mucositis (3.3%). There was a statistically significant difference in mucositis scores at the end of the trial compared with baseline for the topical group (P=<0.001). In the systemic group, zero patients experienced full resolution of symptoms, 11 patients (33.3%) had grade 1 mucositis, nine patients (27.3%) had grade 2, nine patients (27.3%) had grade 3, and four patients (12.1%) experienced grade 4 mucositis. There was no statistically significant difference between mucositis scores at the end of the trial and at baseline for patients treated systemically with vitamin E (P=0.317) (El-Housseiny et al., 2007).

3.7.3 Proposed mechanism of action of vitamin E

A notable omission from the literature concerning vitamin E for the prevention or treatment of mucositis is a proposed mechanism of action. In fact it could be argued that the mechanism of action of interventions for the prevention of mucositis is a much under-researched area. While Sung and colleagues did state that vitamin E may act to prevent mucositis through its function as an antioxidant (Sung et al., 2007), they failed to develop this point further. As vitamin E is a phenolic antioxidant, which through the donation of hydrogen makes free radicals un-reactive (Olson, 2000), it could be hypothesised that the administration of vitamin E to patients receiving chemotherapy could act to reduce the action of the reactive oxygen species produced during the initiation phase of the five-phase model of mucositis (Sonis, 2009). This would therefore limit the damage of the signalling and amplification phase of this model, which would result in a decrease the eventual damage to the oral mucosa. In addition, as vitamin E has anti-inflammatory effects and a role in the regulation of cell proliferation and intracellular signalling, it could be hypothesised that vitamin E could have both role outside its antioxidant function (Olson, 2000). The proposed mechanism of action of vitamin E in the prevention of mucositis requires much more research.

3.8 Conclusion

A number of interventions have been identified in this chapter which have been trialled for the prevention of OM. None of these interventions have been found to be universally beneficial for the prevention of mucositis across different groups of patients. One of the interventions considered was vitamin E. Vitamin E (D-alpha-tocopherol), is cheap, easily obtainable and high doses have not been associated with adverse consistent adverse events. Given its potentially positive effects in the treatment of mucositis, it was deemed appropriate to conduct a non-commercial single site feasibility study to investigate this intervention for the prevention of mucositis.

Before designing a study which aims to explore the feasibility of conducting a future trial with vitamin E for the prevention of mucositis, there are a number of methodological issues that need to be considered:

- How potential biases may affect the quality and interpretation of study results and how these potential biases may be avoided when designing a trial
- What we can learn from reports of previous studies to avoid making the same mistakes, and how the results of previous studies can inform the design of future trials
- What oral assessment instruments are available for use in a clinical trial

The next chapter of this thesis looks at the risk of bias in the studies included in the 2010 Cochrane mucositis prevention review and how the exclusion of studies considered to be at high or unclear ROB reflects the results of the review.

Chapter 4 Risk of Bias in RCTs included in the Cochrane Review of interventions for the prevention of oral mucositis in patients undergoing treatment for cancer

4.1 Introduction

Biases can affect the quality and interpretation of the results. A key aspect of developing a study protocol is a clear understanding of potential biases. Hence this chapter will identify potential biases through the utilisation of the Cochrane ROB instrument and will highlight the areas of methodological development in a study which require further attention.

4.*2* Aim:

To explore the 'Risk of Bias' in studies included in the Cochrane review for the prevention of mucositis and to determine how risk of bias affects the results of the review using a sensitivity analysis.

4.3 What is bias?

A bias is a systematic error in results, which can operate in either direction, leading to an over or underestimation of the effect of the intervention under investigation.

4.4 Types of bias in clinical trials

Table 3 shows the different sources of bias that may be important in clinical trials. The magnitude of these biases can vary.

Table 3: Sources of Bias in Clinical Trials

Type of bias	Domain	Description
Selection bias	Randomisation, Allocation concealment	*"systematic differences between baseline characteristics of the groups that are compared"*
Performance bias	Blinding	*"systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest"*
Detection bias	Blinding	*"systematic differences between groups in how outcomes are determined"*
Attrition bias	Incomplete outcome reporting	*"systematic differences between groups in withdrawals from a study"*
Reporting bias	Selective outcome reporting	*"systematic differences between reported and unreported findings"*

Cochrane Handbook Chapter on ROB (Higgins and Altman, 2009, 8.4a)

The Cochrane Risk of Bias (ROB) instrument assesses the risk of bias in a study across the following eight domains: sequence generation, allocation concealment, blinding of carers, patients and outcome assessors, incomplete outcome data, selective reporting and other.

Random allocation between experimental and control groups is used to give all participants an equal chance of being allocated to either group. It is an attempt to reduce confounding, by ensuring that the groups are well matched for certain variables, for example age or gender. The process of randomisation also minimises selection bias by ensuring that neither trial staff nor the participants themselves are able to predict to which group they will be allocated (Hackshaw, 2009). The method used to randomly allocate participants can be as simple and 'low-tech' as the toss of a coin or the drawing of cards, alternatively, computer randomisation may be favoured in large scale studies, where repeated coin tosses are impractical. Any method of randomisation employed is suitable as long as it has a random component (Higgins and Altman, 2009). Unsuitable methods of sequence generation include allocation based on day of the week, or patient or file number, or date of birth. These methods are additionally unsuitable because it is impossible to conceal the allocation schedule, resulting in foreknowledge of which group a particular participant will be allocated to (Higgins and Altman, 2009).

Adequate randomisation can be undermined by the non-protection of the generated sequence. Adequate allocation concealment prevents the researcher admitting the patients into the trial having foreknowledge of upcoming allocations (Schulz et al., 2002). Inadequate concealment may lead to selective enrolment, with a researcher delaying the allocation of a certain participant until the appropriate allocation slot (Higgins and Altman, 2009). The most desirable method of allocation concealment is probably central allocation by a third party such as a hospital pharmacy. Another method that can be employed is the use of opaque sealed envelopes to conceal the randomisation sequence. However, such a method can be easily abused, if the envelopes are held up to the light, or an envelope is returned to the pile if the initial allocation is not favoured by the researcher. Sequential numbering of envelopes to ensure that patients are allocated in sequence and only opening the envelope after it has been irreversibly allocated to the patient are methods that should be employed in order to reduce the susceptibility of this method to abuse (Higgins and Altman, 2009). The use of drugs containers of identical appearance which are sequentially numbered are another possible method of allocation concealment. In this instance drugs are packed before randomisation, often by an external site, and dispensed to the patients in sequence, therefore reducing selection bias. However, such methods of allocation concealment are only appropriate if the randomisation master list is also concealed. It is pointless to go to the trouble of putting mechanisms in place to protect the allocation sequence, with the use of envelopes or sequentially numbered containers of drugs, and then fail to protect the master list by making it easy for staff to access it. The use of external companies, or pharmacies to generate the randomisation list and then protect it, is a way of getting around this issue. Unsuitable methods of concealment include the posting of the randomisation sequence on a notice board, or the circulation of the sequence between the trial staff by email.

It is easy to mix up allocation concealment with blinding. Allocation concealment protects the generated sequence until the assignment has been made, whereas blinding protects the sequence after the assignment has been assigned (Schulz et al., 2002). It is also always possible to achieve allocation concealment regardless of the intervention (Schulz et al., 2002); however, blinding cannot be implemented in some trials due to the nature of the intervention under investigation (Higgins and Altman, 2009). Blinding is a procedure in whereby the participants, study staff and outcome assessors involved in a

trial are kept oblivious of an allocation after randomisation has taken place (Higgins and Altman, 2009). A lack of patient blinding can influence the assessment of outcome (detection bias) (Juni et al., 2001), either by a lack of expectation in patients in the control arm, or by the potential for a psychological effect arising from participants knowing that they are receiving a new treatment (Schulz et al., 2002). A lack of blinding in outcome assessors may also increase detection bias. If the assessor believed that the new intervention was superior they may, either subconsciously or otherwise, be more generous in their assessments. Blinding in mucositis studies is therefore very important, as these studies may record patient reports of pain or employ subjective methods of mucositis assessment. The employment of blinding also aims to reduces performance bias: the preferential provision of additional treatment interventions to one arm (Schulz et al., 2002). In mucositis trials, an unblinded Clinician may, either consciously or otherwise, administer additional pain relief to patients randomised to receive placebo in a study where the analgesic properties of an intervention are being studied. Similarly, if a patient knew they were receiving the intervention of interest, they may subconsciously not ask for additional pain relief when they need it.

The exclusion of randomised patients from data analysis can result in attrition bias (Gurusamy et al., 2009). Attrition from a study can occur for a variety of reasons. The most obvious is that the patient chooses to withdraw from the study, or was withdrawn due an adverse event. A patient may also fail to attend an outpatient appointment, or to return completed questionnaires or journals. Human error may also result in attrition if a member of staff forgets to complete a relevant form, or loses a completed questionnaire (Higgins and Altman, 2009). Another common reason for attrition is that a patient is subsequently deemed ineligible; due to a change in the planned course of treatment or medication they are to receive (Higgins and Altman, 2009).

Selective outcome reporting is another potential source of bias. This is defined as the selection and reporting of significant results from a sub-section of the available data, in addition to the selective withholding of non-significant studies (Higgins and Altman, 2009). Selective outcome reporting may become apparent when the authors have a range of different time points to choose from, or when there are severe different ways to analyse the data. Mucositis data can be presented in a variety of different ways.

Maximum scores, subset analyses, scores at set time points or area under the curve analyses can all be used to report the results of a study, and the 'cherry picking' of significant analyses together with non reporting of non-significant analyses may bias the study results, and any subsequent meta-analyses. In cross-over studies selective reporting may also be an issue in publications which only report the first period results. Such differences between intervention and control arm may be significant during the first period but not overall, and the reporting of the results in this manner may result in the intervention being mistakenly regarded as efficacious. The authors of the Cochrane handbook suggested that the protocols of included studies should be compared to the resulting publication to determine whether the pre-specified primary and secondary outcomes in the protocol are included in the resulting publication (Higgins and Altman, 2009). However, protocols are rarely available. Therefore, it is the view of the Cochrane Oral Health group that the publication of mucositis grades for all patients included in the analysis is sufficient for an answer of 'yes' for this criterion.

The last assessment in the risk of bias tool is 'other', a catch-all section of any other threats of validity (shown in Table 4). Early stopping is a threat to internal validity. Extreme intervention effects are more likely in studies that have stopped early (Higgins and Altman, 2009). However, such results are not shown in studies that are terminated early due to other issues, such as problems with recruitment or side effects, and these factors are therefore not judged to be at risk of bias. Baseline imbalances in items correlated to the outcome of interest also cause bias in the effect estimate of an intervention (Higgins and Altman, 2009). For example, in a mucositis study, if more patients receiving a particularly mucotoxic drug, such as methotrexate, were randomised to the placebo group, any potential benefit in the prevention of mucositis shown in the intervention group may be a result of bias. Such imbalances may indicate problems with randomisation (Higgins and Altman, 2009).

Unfortunately, scientific fraud is another potential threat to the internal validity of a study. Recently, Chinese studies have been an area of concern, as reviews have reported that Chinese herbal medicine studies reported in Chinese have shown considerably larger effect sizes than those reported in English (Shang et al., 2007), and that some Chinese medicine trials have not employed an adequate placebo comparator (Qi et al.,

2008). However, most concerning of all is the suggestion that some Chinese herbal medicine and western medicine studies conducted in China, which claim to be RCTs, are not actually 'true' RCTs at all, and that the term "randomised" had been misused by the authors (Wu et al., 2009b). As it is near impossible to distinguish between legitimate RCTs and these fraudulent studies The Cochrane Oral Health group feels it has no option but to classify all studies conducted in China at high ROB in the 'other' category.

Table 4: Other Potential Threats to Validity

Other potential threat to validity
Early stopping
Baseline imbalance
Blocked randomization in unblinded trials
Selective reporting
Interim results
Fraud
Deviation from the study protocol
Administration prior to randomisation of an intervention that could increase or reduce the effect of the subsequent randomized products
Administration of an intervention or a co-intervention considered to be inappropriate
Inappropriate influence of funders
Contamination

Amended from the Cochrane Handbook (Higgins and Altman, 2009)

4.5 Methods:

The full texts of all new and previously included studies in the Cochrane prevention review (Worthington et al., 2010) were assessed by the researcher (GB) for risk of bias (ROB) in eight categories (adequate sequence generation, allocation concealment, blinding of carers, patients and outcome assessors, income outcome data, free of selective bias and other) using the assessment rules shown Table 5. This work was undertaken as part of an update of the review.

Table 5: Assessment Rules

Sequence generation	Yes	• "Reference to a random number table". • "Use of a computer number generation" • "Tossing coins" • "Shuffling envelopes" • "Minimization"
	No	• "Allocation based on birth date" • "Allocation based on physician judgement" • "Allocation based on hospital number or some other rule"
	Unclear	• "Insufficient information to make a judgement of either 'yes' or 'no'"
Allocation concealment	Yes	• "Central method of allocation" • "Drug containers of identical appearance which are sequentially numbered" • "Opaque sequentially numbered envelopes"
	No	• "Use of an open allocation list" • "Assignment envelopes without appropriate safeguards" • "Alternation or rotation"
	Unclear	• "Insufficient information to make a judgement of either 'yes' or 'no'"
Blinding	Yes	• "Blinding of participants and key personnel. Unlikely that this blinding could have been broken" • "Participants or key study personnel are unblinded and the non blinding of others was unlikely to introduce bias"
	No	• "No or incomplete blinding. Outcome of interest is likely to be influenced by a lack of blinding" • "Blinding described. However, it is likely that blinding could be broken".
	Unclear	• "Insufficient information to make a judgement of either 'yes' or 'no"
Incomplete outcome data	Yes	• "No missing outcome data" • "Missing outcome data balanced across arms. Both groups have similar reasons for missing data." • "Dichotomous outcomes: The proportion of missing data are insufficient to have a clinically meaningful impact on the intervention effect estimate."
	No	• "Imbalance between arms for missing data or withdrawals." • "Dichotomous outcomes: The proportion of missing data are enough to have a clinically meaningful impact on the intervention effect estimate."
	Unclear	• "Insufficient information to make a judgement of either 'yes' or 'no"
Selective outcome reporting	Yes	• "Study protocol is available and when compared with the publication, all outcomes of interest have been reported in the manner which was pre-specified" • "Study protocol is not available, however it is clear that all expected outcomes are reported (mucositis incidence by grade)"
	No	• "One or more reported outcome measures have been reported incompletely and therefore cannot be entered into the meta-analysis." • "One or more reported primary outcomes were not pre-specified."
	Unclear	• "Insufficient information to make a judgement of either 'yes' or 'no'"

Assessment rules amended from the Cochrane Handbook (Higgins and Altman, 2009, 8.5.c).

After the initial assessment for ROB, GB then divided the articles between members of the Cochrane Oral mouth-care group (AMG, HW, JC, SF, TW) for second assessment. Initial and secondary assessments were compared and in the event of differences of opinion a dialogue was established between the researchers. Unresolved differences were taken to a third party. In order to determine the impact of the ROB on the results of the prevention review a sensitivity analysis was conducted with only the studies judged to be at low risk of bias for allocation concealment and blinding of outcome assessors. Outcome assessor blinding was selected as a key domain because a lack of blinding has been reported to significantly influence effect size: Juni and colleagues reported that open outcome assessment influenced effects size by 35% (95% CI 1% to 57%) (P=0.046) in a meta-analysis which compared the use of low weight heparin to standard heparin for the prevention of post-operative thrombosis (Juni et al., 1999). Allocation concealment was chosen as a key domain because effect sizes have been found to be exaggerated in studies with subjective outcomes (Wood et al., 2008). As the assessment of mucositis is subjective, this was considered an appropriate key domain.

Sensitivity analyses were first conducted for each domain independently in order to explore the effect of each of the key domains on the results of the prevention review. It was considered that this would provide a greater understanding of the impact of adequate allocation concealment and outcome assessor blinding on the results of the review and might help explain the results of the overall ROB sensitivity analysis. The full version of the Cochrane prevention review used fixed effects measures for meta-analyses which include less than four studies and random effects measures for meta-analyses with more than four studies. The sensitivity analyses were therefore conducted using these rules.

There are a number of methods for presenting the overall risk of bias. This can be done for each study, for each intervention and for the results of the review overall. The Cochrane handbook suggested defining the ROB for each study based on ROB assessments from key domains. Adequate allocation concealment and outcome assessor blinding were identified as key domains for assessing overall ROB prior to conducting the sensitivity analysis. Overall ROB was determined for each study in the review using the grading rules shown in Table 6.

Table 6: Overall Risk of Bias Criteria

Low	Low ROB (judgement of yes) for both the allocation concealment and outcome assessor blinding domains
Unclear	Judgement of unclear for either allocation or outcome assessor blinding domains
High	High ROB (judgement of no) for either allocation concealment or outcome assessor domains

Amended from the Cochrane Handbook (Higgins and Altman, 2009, 8.7a)

4.6 Results:

The risk of bias was assessed for the 130 studies (43 interventions) included in the 2010 update of the review (Worthington et al., 2010). The brief results of these assessments are shown in Table 7.

Table 7: Risk of Bias Results

Author	Intervention	Adequate sequence generation	Allocation Concealment	Blinding		Outcome assessor	Incomplete outcome data addressed	Free of selective bias	Free of other bias	Overall risk of bias
				Carer	Patient					
Bubley, 1989	Acyclovir	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Abbasi Nazari, 1989	Allopurinol	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear
Dozono, 2007	Allopurinol	Unclear	Unclear	No	No	No	Yes	Yes	No	High
Loprinzi, 1990	Allopurinol	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Panahi, 2010	Allopurinol	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Puataweepong, 2009	Aloe Vera	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Su et al, 2004	Aloe Vera	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
Antonadou, 2002	Amifostine	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Bourhis, 2000	Amifostine	Unclear	Yes	No	No	No	Yes	Unclear	Unclear	High
Brizel, 2000	Amifostine	Yes	Yes	No	No	No	Yes	Unclear	Yes	High
Buentzel, 2006	Amifostine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Buntzel, 1998	Amifostine	Unclear	Unclear	No	No	No	Yes	Yes	No	High
Haddad, 2009	Amifostine	Yes	Yes	No	No	No	Yes	Unclear	Yes	High
Hartmann,2001	Amifostine	Unclear	Unclear	No	No	No	Yes	Unclear	Yes	High
Koukourakis, 2000	Amifostine	Yes	No	No	No	No	Unclear	Unclear	Yes	High
Spencer, 2005	Amifostine	Unclear	Unclear	No	No	No	Yes	Unclear	Yes	High
Vacha 2003	Amifostine	Unclear	Unclear	No	No	No	Yes	Unclear	Yes	High
Veerasarn, 2006	Amifostine	Unclear	Unclear	No	No	No	Unclear	Unclear	Yes	High
El-Sayed, 2002	Antibiotic pastille or paste	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Stokman, 2003	Antibiotic pastille or paste	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low

Author	Intervention	Adequate sequence generation	Allocation Concealment	Blinding			Incomplete outcome data addressed	Free of selective bias	Free of other bias	Overall risk of bias
				Carer	Patient	Outcome assessor				
Symonds, 1996	Antibiotic pastille or paste	Unclear	Unclear	Yes	Yes	Yes	No	Unclear	Yes	Unclear
Wijers, 2001	Antibiotic pastille or paste	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear
Epstein 1989	Benzydamine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Epstein 2001	Benzydamine	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear
Kazemian, 2009	Benzydamine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Prada, 1987	Benzydamine	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear
Mills, 1988	Beta-carotene	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Fidler, 1996	Chamomile	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Gandemer, 2007	Chewing gum	Yes	Yes	No	No	No	Yes	Unclear	Yes	High
Huang, 2003	Chinese medicine	Yes	No	No	No	Unclear	Yes	Yes	No	High
Wang, 2002	Chinese medicine	Unclear	Unclear	No	No	Unclear	Yes	Unclear	No	Unclear
Dodd, 1996	Chlorhexidine	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	Yes	Unclear
Ferretti, 1988	Chlorhexidine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Foote, 1994	Chlorhexidine	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
McGaw, 1985	Chlorhexidine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Pitten, 2003	Chlorhexidine	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No	Low
Sorensen, 2008	Chlorhexidine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Spijkervet, 1989	Chlorhexidine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Wahlin, 1989	Chlorhexidine	Unclear	Unclear	No	No	No	Unclear	Unclear	No	High
Yuen, 2001	Clarithromycin	Yes	Unclear	No	No	No	Yes	Unclear	Yes	High
Cascinu, 1994	Cryotherapy	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Gori, 2007	Cryotherapy	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Lilleby, 2006	Cryotherapy	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Mahood, 1991	Cryotherapy	Unclear	Unclear	No	No	Unclear	Yes	Yes	Yes	Unclear
Rocke, 1993	Cryotherapy	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Svanberg, 2007	Cryotherapy	Unclear	Unclear	No	No	No	Yes	Unclear	Yes	High

Author	Intervention	Adequate sequence generation	Allocation Concealment	Blinding			Incomplete outcome data addressed	Free of selective bias	Free of other bias	Overall risk of bias
				Carer	Patient	Outcome assessor				
Qin 2007	Dental stent	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear
Wu, 2009	Epidermal growth factor	Unclear	Unclear	No	No	No	Yes	Unclear	Yes	High
Crawford, 1999	G-CSF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Katano, 1995	G-CSF	Unclear	Unclear	No	No	No	Yes	Unclear	Yes	High
Schneider, 1999	G-CSF	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	No	Low
Su, 2006	G-CSF	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low
Anderson, 1998	Glutamine	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear
Cerchietti, 2006	Glutamine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Choi, 2007	Glutamine	Yes	Unclear	No	No	No	Yes	Yes	Yes	High
Coghlin-Dickson, 2000	Glutamine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
He, 2008	Glutamine	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	No	Unclear
Huang, 2000	Glutamine	Unclear	Unclear	Unclear	Yes	No	Yes	Yes	Yes	High
Jebb, 1994	Glutamine	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Unclear
Li, 2006	Glutamine	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear
Okuno, 1999	Glutamine	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No	Unclear
Sornsuvit, 2008	Glutamine	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Unclear
Cartee, 1995	GM-CSF	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Chi 1995	GM-CSF	Unclear	Unclear	Unclear	No	No	Yes	Unclear	Yes	High
Dazzi, 2003	GM-CSF	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Ifrah, 1999	GM-CSF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Unclear
Makkonen, 2000	GM-CSF	Yes	Yes	No	No	No	Yes	Unclear	Yes	High
McAleese, 2006	GM-CSF	Unclear	Unclear	Unclear	No	Yes	Yes	Yes	Yes	Unclear
Nemumaitis, 1995	GM-CSF	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	No	Unclear
Saarilahti, 2002	GM-CSF	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Van der Lelie, 2001	GM-CSF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Elad, 2006	Histamine Gel	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Yes	Unclear

Author	Intervention	Adequate sequence generation	Allocation Concealment	Blinding			Incomplete outcome data addressed	Free of selective bias	Free of other bias	Overall risk of bias
				Carer	Patient	Outcome assessor				
Biswal, 2003	Honey	Yes	Unclear	No	No	No	Yes	Unclear	Yes	High
Motallebnejad 2008	Honey	Unclear	Unclear	Unclear	No	Yes	Yes	Unclear	Yes	Unclear
Rashad, 1984	Honey	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Dorr, 2007	Hydrolytic enzymes	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Gujral, 2001	Hydrolytic enzymes	Unclear	Unclear	No	No	No	Yes	Yes	Yes	High
Kaul, 1999	Hydrolytic enzymes	Unclear	Unclear	No	No	No	No	Unclear	Yes	High
You, 2009	Indigowood root	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear
Peterson, 2009	Intestinal trefoil factor	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Unclear
Giles, 2004	Iseganan	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear	Yes	Unclear
Trotti, 2004	Iseganan	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Blazar, 2006	Keratinocyte GF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Brizel, 2008	Keratinocyte GF	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	No	Unclear
Freytes, 2004	Keratinocyte GF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear
Meropol, 2003	Keratinocyte GF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Rosen, 2006	Keratinocyte GF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Spielberger, 2004	Keratinocyte GF	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Antunes, 2007	Laser	Unclear	Unclear	Yes	Yes	No	Yes	Yes	Yes	High
Arun-Maiya, 200	Laser	Yes	Unclear	No	No	Yes	Yes	Yes	Unclear	Unclear
Bensadoun, 1999	Laser	Yes	Unclear	Yes	Yes	Yes	Yes	Unclear	Unclear	Unclear
Chor, 2009	Laser	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Cruz, 2007	Laser	Unclear	Unclear	No	No	Yes	Yes	Yes	Yes	Unclear
Schubert, 2007	Laser	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Unclear
Borowski, 1994	Oral care	Unclear	Yes	No	No	No	Yes	Unclear	Yes	High
Shieh, 1997	Oral care	Yes	Unclear	No	No	No	Yes	Unclear	No	High

Author	Intervention	Adequate sequence generation	Allocation Concealment	Blinding			Incomplete outcome data addressed	Free of selective bias	Free of other bias	Overall risk of bias
				Carer	Patient	Outcome assessor				
Attal, 1993	Pentoxifylline	Yes	Yes	No	No	Unclear	Yes	Unclear	Yes	Unclear
Lockhart, 2005	Pilocarpine	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Scarantino, 2006	Pilocarpine	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear
Watanabe, 2010	Polaprezinc	Unclear	Unclear	No	No	No	Yes	Yes	No	High
Madan 2008	Povidone-iodine	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Rahn, 1997	Povidone-iodine	Unclear	Unclear	No	No	No	Unclear	Yes	Unclear	High
Vokurka, 2005	Povidone-iodine	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Leborgne, 1998	Prednisone	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Ahmed, 1993	Propantheline	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Unclear
Duenas-Gonzalez, 1996	Prostaglandin	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Unclear
Hanson,1995	Prostaglandin	Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear	No	Unclear
Labar, 1993	Prostaglandin	Yes	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
Pillsbury, 1986	Prostaglandin	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
Veness, 2006	Prostaglandin	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Bjarnason, 2009	Radiation: morning v evening	Yes	Unclear	No	No	No	Yes	Unclear	Yes	High
Goyal, 2009	Radiation: morning v evening	Unclear	Unclear	No	No	Yes	No	Yes	Yes	Unclear
Hu, 2005	Shenqi-Fanghou	Unclear	Unclear	No	No	Unclear	Yes	Yes	No	Unclear
Tu 1998	SOD	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Unclear
Carter, 1999	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Unclear
Castagna, 2001	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	Unclear
Cengiz, 1999	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear
Epstein and Wong, 1994	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Evensen, 2001	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Franzen, 1995	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear

Author	Intervention	Adequate sequence generation	Allocation Concealment	Blinding			Incomplete outcome data addressed	Free of selective bias	Free of other bias	Overall risk of bias
				Carer	Patient	Outcome assessor				
Lievens, 1998	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Unclear	Unclear	Yes	Unclear
Makkonen, 1994	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	No	Unclear
Nottage, 2003	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Unclear	Unclear
Pfeiffer, 1990	Sucralfate	Unclear	Unclear	Unclear	Yes	Yes	No	Unclear	No	Unclear
Scherlacher, 1990	Sucralfate	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	Unclear
Shenep, 1988	Sucralfate	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Yes	Low
Oberbaum, 2001	Traumeel S	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	No	Unclear
Dai, 2009	Yangygin-Humo decoctalion	Unclear	Unclear	No	No	No	Yes	Yes	No	High
Ertekin, 2004	Zinc sulphate	Unclear	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear
Lin, 2006	Zinc sulphate	Yes	Unclear	Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear

4.6.1 Results by domain

4.6.1.1Adequate sequence generation

Twenty-six studies (20%) were deemed to have adequate sequence generation, and therefore were classified as being at low risk of bias for this domain. Twelve of these studies employed computer-based sequence generation; while, four studies employed minimization, an often complex process in which treatment arms are balanced for a number of pre-specified criteria. Four studies did not provide enough information about the randomisation process; however it was the opinion of the assessors that the setting of these trials made adequate randomisation likely. These studies were conducted at the Dana Faber cancer institute (Haddad et al., 2009), the Memorial Sloan Kettering Cancer Centre (Su et al., 2004), the Duke Centre (Cartee et al., 1995) and the Finnish cancer registry (Makkonen et al., 2000). One study used biased coin randomisation (Su et al., 2004). Of the remaining five studies, three used a table of random numbers (Huang et al., 2003, Koukourakis et al., 2000, Pitten et al., 2003), and two studies provided limited information but made reference to appropriate literature concerning randomisation (Brizel et al., 2000, Shieh et al., 1997). Those studies considered to use an inappropriate method of randomisation were removed from the publication as per the exclusion criteria; therefore no studies were given a decision of no for this category. The remaining 104 studies (80%) were judged as 'unclear'. The majority of these unclear studies gave no more information than that they were 'randomised'. Four studies stated that they employed the "closed envelope" method of randomisation. However, no information was provided about whether these envelopes were shuffled prior to the patient being randomised. They were therefore classified as "unclear".

4.6.1.2 Adequate allocation concealment

Seventeen studies (13%) employed adequate methods of allocation concealment and were therefore classified as being at low risk of bias. Central randomisation was mentioned in 15 studies, with seven studies employing pharmacy controlled randomisation, six studies communicating by telephone, and one study by fax (Gandemer et al., 2007). Two studies employed drug containers which were identical in appearance and sequentially numbered (Foote et al., 1994, Madan et al., 2008). Two studies (1.5%) used open number tables without concealment and were

therefore deemed to be a high risk of bias (Huang et al., 2003, Koukourakis et al., 2000). The remaining 111 studies (85%) were classified as unclear.

4.6.1.3 Blinding

Blinding was assessed for three different groups: patients, carers and outcome assessors. Nineteen studies (15%) were deemed to be at low risk of bias for carer blinding. Forty-four studies (34%) were classified as being at high risk of bias. Sixty-seven (51%) studies were classified as 'unclear'. Seventy-five studies (58%) were deemed to be at low risk of bias for patient blinding. Ten studies (7.7%) were classified as unclear. Of these studies, four were deemed unclear as they employed the use of a placebo control, and therefore blinding could not be discounted, while three studies were assessed for ROB from a data collection sheet provided by a translator without any additional information. Of the remaining three 'unclear' studies, one study which compared povidone-iodine to saline was described as 'blind' to patients, however, this was considered by the assessors to be an inappropriate control as presumably the iodine solution would differ in colour from the saline (Vokurka et al., 2005). Another, which investigated zinc in head and neck patients receiving a mix of radiotherapy and chemoradiotherapy (Ertekin et al., 2004), was classified as unclear for two reasons: firstly, because the study authors described the need for a double blind study in the introduction, and then failed to provide any information about blinding in the remainder of the text, and secondly, because the authors used empty capsules as the control, and the assessors were concerned that this would be noticeable to the patients. The remaining trial (Ahmed et al., 1993) only stated that "trial drugs were administered blind" (Ahmed et al., 1993, 131), without any additional information. Forty-five studies (35%) were classified as being at high risk of bias for patient blinding. The majority of these were studies which employed no blinding, however one study was described by its authors as double blind, but then went on to state that a patient withdrew from the study because they were not allocated the intervention of interest (Wu et al., 2009a). The assessors were concerned that this suggested a failure in the blinding of patients in this study, and therefore decided to characterise the study at high risk of bias for all three blinding categories.

Seventy-seven studies (59%) were deemed to describe the method of outcome assessor blinding adequately and were considered to be at low risk of bias. Sixteen studies (12%) were classified as unclear and 37 studies (29%) were given a decision of 'no' and were therefore considered to be at high risk of blinding in this category. In a sub-analysis of those studies providing blinding information, only 19 studies (24.6%) gave specific information regarding the blinding of an outcome assessor. The remaining 58 (75%) studies were only described as "double blind" by the authors.

4.6.1.4 Incomplete outcome data addressed

One hundred and seven studies (82%) were considered to be at low risk of bias for this category. Eighteen studies (14%) were given a decision of unclear and five (3.8%) were considered to be at high risk of bias. These five studies experienced a high rate of drop-out and the authors did not provide an adequate explanation of why data from these patients were excluded.

4.6.1.5 Free of selective reporting

Forty eight (37%) studies were deemed to be free of selective reporting for mucositis grade, which was determined prior to assessment as the outcome of interest for this category. These studies were therefore deemed to be at a low risk of bias. The remaining eighty-two studies were classified as unclear. These studies tended to only provide sub-sets of data for severe mucositis (grade>2) rather than all the information of interest. No studies were given a decision of 'no', and consequently classified at high risk of bias, as studies which did not provide mucositis information for at least one of the dichotomies of interest could not be included in the review.

4.6.1.6 Free of other bias

Thirty-six studies (28%) were deemed to be at high risk of bias in the final "other" category. A baseline imbalance was reported by 11 studies. Three studies reported gender imbalances (Abbasi Nazari et al., 2007, Makkonen et al., 1994, Puataweepong et al., 2009), while four studies reported age imbalances (Bensadoun et al., 1999, Ifrah et al., 1999, Makkonen et al., 1994). Two or more baseline imbalances were reported by four studies (Bensadoun et al., 1999, Ifrah et al., 1999, Makkonen et al., 1994,

Puataweepong et al., 2009). Puataweepong and colleagues (2009), reported baseline imbalances in both patient gender (P=0.03) and previous surgery (P=0.04). Meanwhile, in the Ifrah study (1999), patients randomised to receive GM-CSF in the intervention arm of the study, were older (P=0.04) and more likely to have the Philadelphia chromosomal rearrangement (P=0.026). Baseline imbalances in age and gender were reported by Makkonen and colleagues (Makkonen et al., 1994). Bensadoun and colleagues (1999), reported imbalances in the number of patients receiving supplementary application of laser to the neck, which was hypothesised to exert a distant beneficial effect. In this study patients in the intervention group also tended to be older. However, no P values were presented by the authors for this imbalance (Bensadoun et al., 1999). Risk of bias was assessed for eight studies from a data collection form completed by a translator. Loprinzi and colleagues (1990), initially aimed to recruit 120 patients into their allopurinol study, however, the power calculation was re-run after 77 patients and as the results were found to favour the intervention, the study was terminated and the data published. In the Duenas-Gonzalez and colleagues study (1996), an interim analysis conducted in the 16 patients recruited into the study showed a significant difference in favour of the placebo, and the authors therefore decided to cease recruitment. Epstein and Wong (1994), also report the results of an interim analysis, in this case a trial of 33 patients which compared sucralfate to placebo. This trial was terminated after an interim analysis suggested that the impact of sucralfate on mucositis prevention was minimal (Epstein and Wong, 1994).

4.6.2 Sensitivity analysis based on individual ROB domains:

4.6.2.1 Allocation concealment

If studies lacking adequate allocation concealment are excluded from the review, the results are notably altered. Firstly, such exclusions removed 114 studies (87%), and 33 interventions (77%), from the results of the publication. Perhaps more importantly, eight of these excluded interventions were previously found to be statistically significant in the results of the meta-analysis update (Worthington et al., 2010). Of the remaining 17 studies, three were interventions either comprised of only one study (Attal et al., 1993, Gandemer et al., 2007), or which only had data from one study available at each dichotomy (Borowski et al., 1994). In addition, one intervention, povidone-iodine, cannot be discussed in the sensitivity analysis as the only study assessed to be at low ROB for allocation concealment was a text only inclusion (Madan et al., 2008). The

results of these studies which were reported in the single studies or text only tables of the review, rather than as a meta-analysis, do not change, and will therefore not be discussed.

Table 8 details the results of the sensitivity analysis compared to the results of the review. Interventions which became statistically beneficial after the removal of studies assessed to be at high or unclear ROB are highlighted in green. Interventions which moved from significant to non-significant are highlighted in yellow.

Table 8 : Impact of the Removal of Studies Judged to be at High or Unclear ROB for Allocation Concealment on Results[1]

Intervention	Dichotomies	Analysis including all studies		P value	Analysis excluding studies at high or unclear ROB		P value
		N	(RR (95% CI)		N	(RR (95% CI)	
Amifostine	Any mucositis	3	0.95 (0.91, 0.99)	0.007	0	-	-
	Moderate to severe	6	0.78 (0.62, 0.98)	0.03	1	1.03 (0.83, 1.28)	0.80
	Severe	9	0.68 (0.45, 1.03)	0.07	1	1.76 (1.01, 3.07)	0.05
Antibiotic pastille / paste	Any mucositis	3	0.92 (0.85, 0.99)	0.03	0	-	-
	Moderate to severe	2	0.92 (0.78, 1.08)	0.32	0	-	-
	Severe	3	0.87 (0.71, 1.07)	0.19	1	0.87 (0.70, 1.10)	0.24
Chlorhexidine	Any mucositis	4	0.76 (0.47, 1.24)	0.27	1	1.04 (0.93, 1.15)	0.50
	Moderate to severe	3	0.93 (0.72, 1.21)	0.58	2	1.42 (1.05, 1.93)	0.02
	Severe	4	0.82 (0.54, 1.23)	0.33	1	1.01 (0.62, 1.64)	0.97
GCSF	Any mucositis	4	0.77 (0.48, 1.23)	0.27	2	1.04 (0.83, 1.32)	0.79
	Severe	2	0.36 (0.15, 0.86)	0.02	2	0.36 (0.15, 0.86)	0.02
GM-CSF	Any mucositis	2	0.93 (0.84, 1.04)	0.21	1	0.91 (0.80, 1.04)	0.16
	Moderate to severe	2	0.89 (0.76, 1.05)	0.17	0	-	-
	Severe	6	0.73 (0.39, 1.40)	0.35	2	1.02 (0.52, 1.99)	0.96
Sucralfate	Any mucositis	4	1.03 (0.96, 1.11)	0.42	0	-	-
	Moderate to severe	5	0.83 (0.59, 1.18)	0.30	1	0.94 (0.67, 1.33)	0.75
	Severe	8	0.74 (0.54, 1.01)	0.06	1	0.33 (0.10, 1.07)	0.06

[1] Interventions which became statistical beneficial after the removal of studies assessed to be at high or unclear ROB are highlighted in green. Interventions which moved from significant to non-significant are highlighted in yellow.

4.6.2.1.1 Amifostine

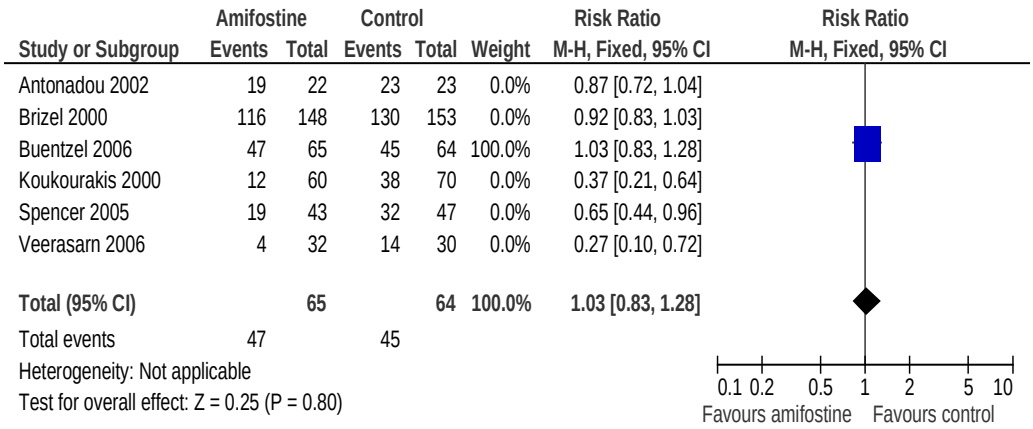


Figure 5: Amifostine 'Moderate Plus Severe' Mucositis Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

In the review update, amifostine was found to significantly prevent mucositis compared to placebo or no treatment in the 'any' and 'moderate to severe dichotomies'. However, all three studies included in the amifostine 'any mucositis' dichotomy in the review were assessed as being at high ROB, and therefore this dichotomy was excluded from the sensitivity analysis. The exclusion of studies assessed at high ROB in the moderate to severe dichotomy changed the risk ratio from 0.78 (95% confidence intervals (CI) 0.62, 0.98) to 1.03 (95% CI 0.83, 1.28) (Figure 5). The exclusion of the studies assessed at high ROB for allocation concealment from the 'severe' mucositis dichotomy changed the result to significantly favour the control group and changes the risk ratio from 0.68 (0.45, 1.03) to 1.76 (1.01, 3.07) (P=0.05) (Figure 6).

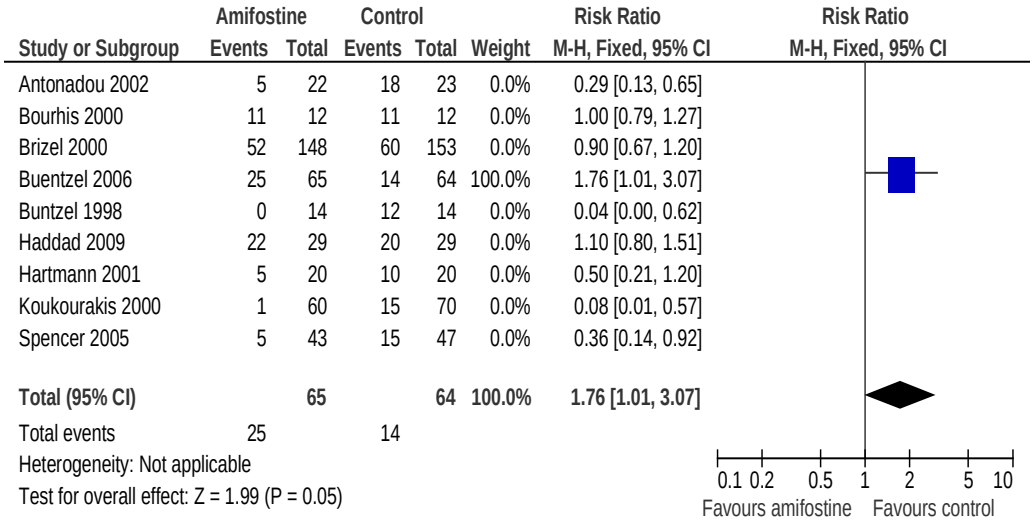


Figure 6: Amifostine 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

4.6.2.1.2 Antibiotic pastille or paste

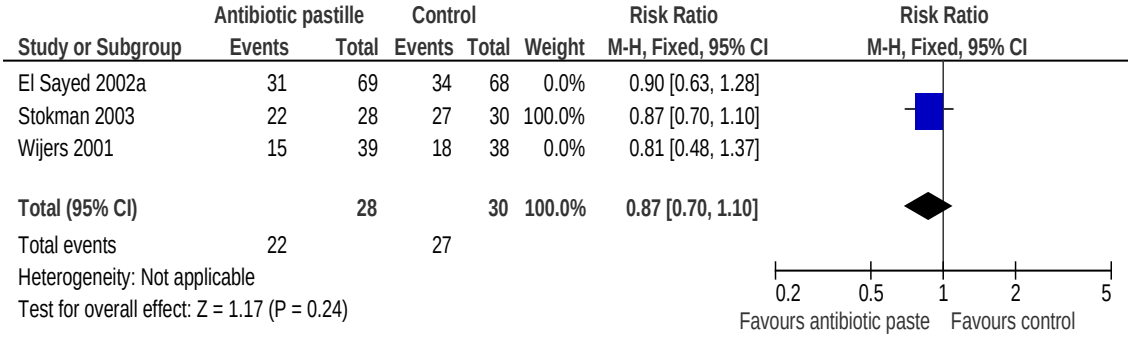


Figure 7: Antibiotic Pastille or Paste 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

Four studies were included in the prevention review comparing an antibiotic pastille or paste to either a placebo or no-treatment and this intervention was found to be significant in the "any mucositis" dichotomy compared to either a control or no treatment. When the ROB assessments are incorporated (Figure 7), data were only available for the severe mucositis dichotomy and no statistically significant differences were found.

4.6.2.1.3 Chlorhexidine

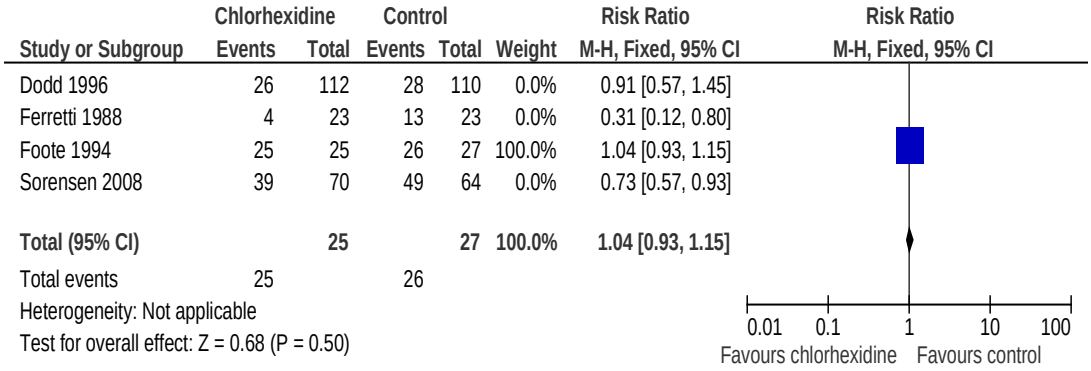


Figure 8: Chlorhexidine 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

Limiting the meta-analysis to include only studies assessed as being at low risk of bias for allocation concealment removed four studies from the sensitivity analysis. Consequently, this changed the risk ratio from 0.76 (95% confidence intervals (CI) 0.47, 1.24) to 1.04 (95% CI 0.93, 1.15) for the prevention of 'any' mucositis (Figure 8).

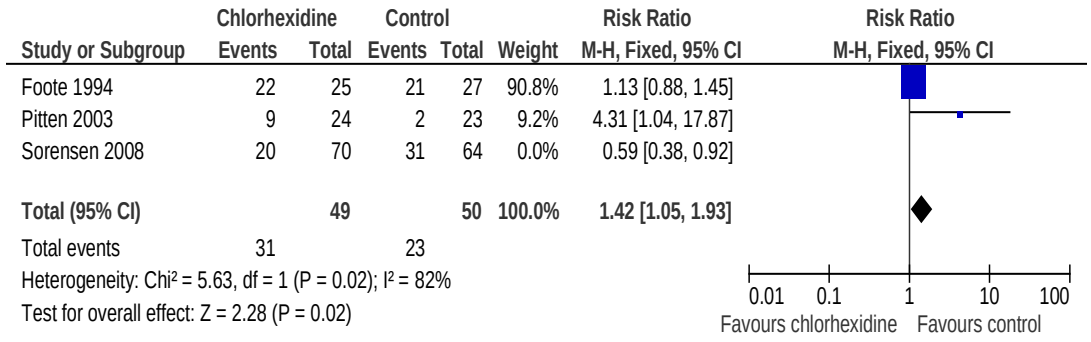


Figure 9: Chlorhexidine 'Moderate to Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

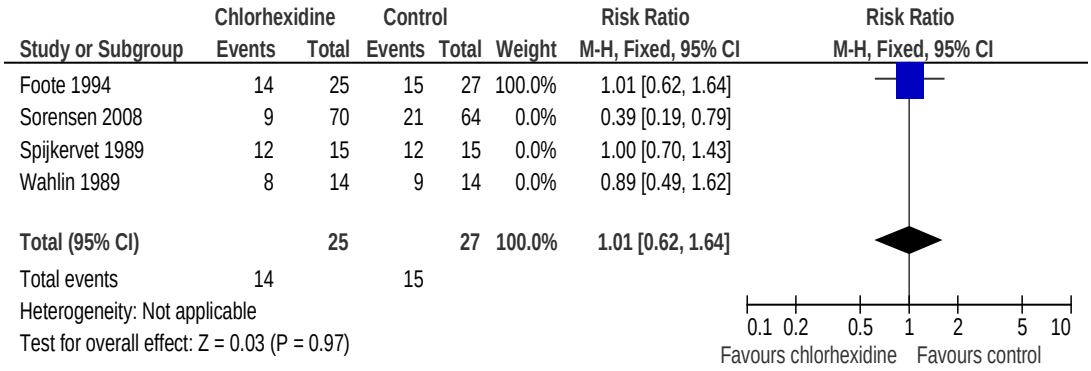


Figure 10: Chlorhexidine 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

The removal of studies without adequate allocation concealment significantly altered the risk ratio in favour of the control in the moderate mucositis dichotomy, from 0.93 (95% CI 0.72, 1.21) to 1.42 (95% CI 1.05, 1.93) (Figure 9). The risk ratio for the prevention of severe mucositis are also altered from 0.82 (95% CI 0.54, 1.23) to 1.01 (95% CI 0.62, 1.64) (Figure 10).

4.6.2.1.4 G-CSF

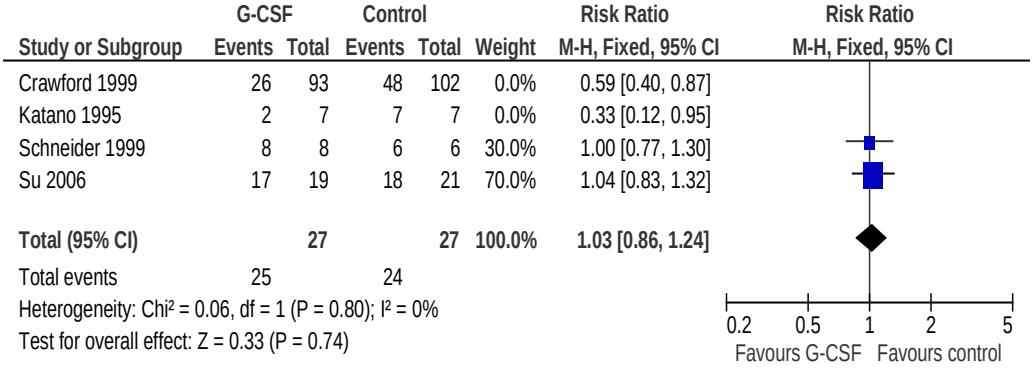


Figure 11: G-CSF 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

Four studies included in the full version of the prevention review compared the use of G-CSF to no treatment, and data were provided by more than one study for two dichotomies: any mucositis and severe mucositis. Two of these studies were judged to be at low ROB for allocation concealment (Schneider et al., 1999, Su et al., 2006). The exclusion of the high and unclear ROB studies altered the risk ratio for the prevention of

'any' mucositis from 0.77 (95% CI 0.48, 1.23) to 1.02 (95% CI 0.86, 1.24) (Figure 11). Data were only provided for one study in the 'moderate to severe' dichotomy, and two studies in the 'severe mucositis' dichotomy, and as all these studies were assessed to be at low ROB for allocation concealment the result of these meta-analysis were unchanged.

4.6.2.1.5 GM-CSF

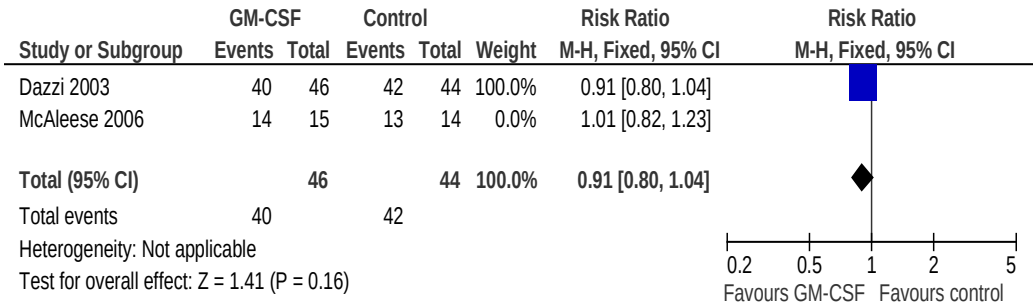


Figure 12: GM-CSF 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

Of the seven studies included in the original prevention review analysis for GM-CSF, one compared GM-CSF to sucralfate (Saarilahti, 2002) and was included in the single studies table. Of the remaining studies, three were judged to be at low ROB for allocation concealment. The exclusion of the other studies marginally altered the risk ratio for the 'any mucositis' dichotomy from 0.93 (95% CI 0.84, 1.04) to 0.91 (95% CI 0.80, 1.04) (Figure 12). No studies providing data in the moderate to severe dichotomy were assessed to be at low risk of bias, and this dichotomy was therefore removed from the sensitivity analysis. The risk ratio for the prevention of severe mucositis was altered from 0.73 (95% CI 0.39, 1.40) to 1.00 (95% CI 0.60, 1.67) (Figure 13).

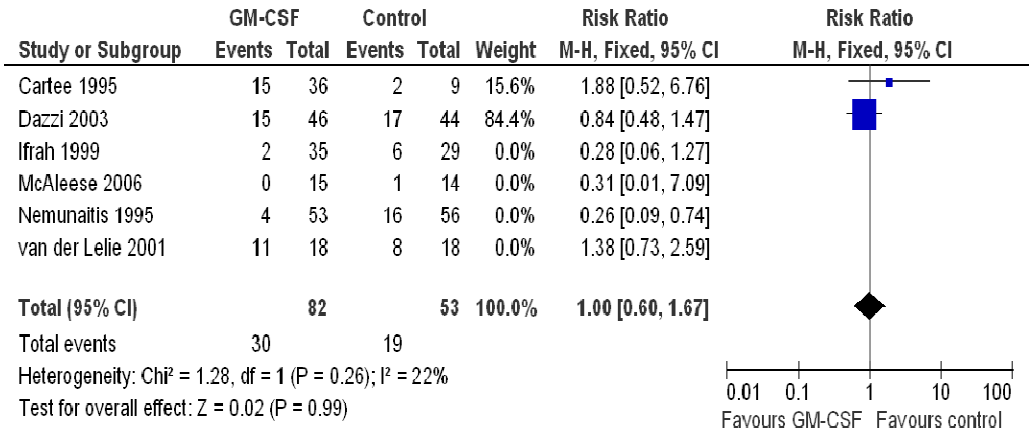


Figure 13: GM-CSF 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

4.6.2.1.6 Sucralfate

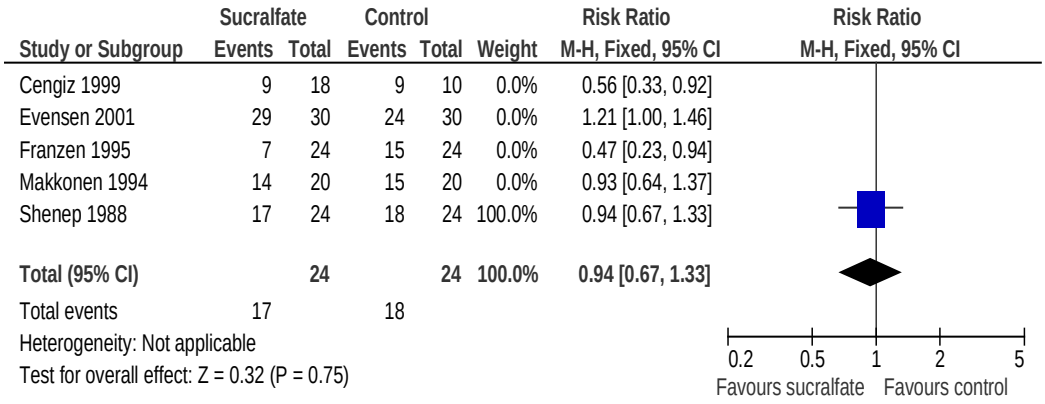


Figure 14: Sucralfate 'Moderate to Severe mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment

Of the ten studies included in the sucralfate meta-analysis in the full review only one study was assessed to be at low risk of bias for allocation concealment. No studies providing data in the 'any mucositis' dichotomy were assessed to be at low risk of bias, and this dichotomy was therefore removed from the sensitivity analysis. The exclusion of the other studies marginally altered the risk ratio for the 'mild to severe' dichotomy from 0.83 (95% CI 0.59, 1.18) to 0.94 (95% CI 0.67, 1.33) (Figure 14). The risk ratio for the prevention of severe mucositis was also altered from 0.74 (95% CI 0.54, 1.01) to 0.33 (95% CI 0.10, 1.07) for the prevention of severe mucositis (Figure 15).

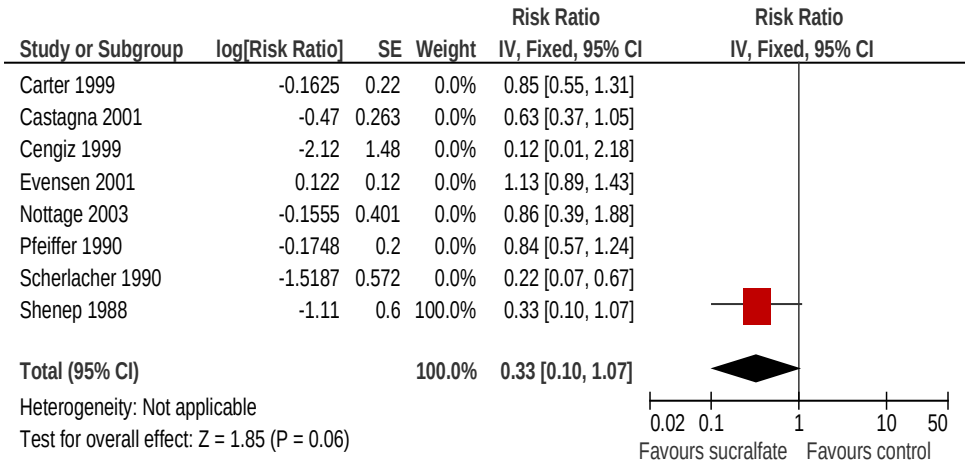


Figure 15: Sucralfate 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Allocation Concealment[2]

4.6.2.2 Outcome assessor blinding

Studies deemed to be at high or unclear risk of bias for outcome assessor blinding were removed from the analyses, leaving 26 interventions, comprising 77 studies, in the meta-analysis. Seven of these interventions (Acyclovir, Chamomile, Histamine gel, Intestinal Trefoil factor, Prednisone, SOD, Traumeel S.) were comprised of only one study and were therefore unchanged. The results from the meta-analysis of laser versus povidone were also unchanged (Arun Maiya et al., 2006). The results of an additional eight interventions (Aloe vera, Antibiotic pastille or paste, Benzydamine, Iseganan, Keratinocyte growth factor, Prostaglandin and Pilocarpine) were unchanged due to all included studies being assessed at low risk of bias for outcome assessment. Another intervention, povidone-iodine, cannot be discussed in the sensitivity analysis as the only study assessed to be at low ROB for outcome assessor blinding was a text only inclusion (Madan et al., 2008). Finally, one intervention, hydrolytic enzymes, was not included in the sensitivity analysis as the substantial level of heterogeneity identified in the prevention review meta-analysis prevented the pooling of data for this intervention. Table 9 details the results of the sensitivity analysis compared to the results of the review.

[2] Generic inverse variance method used as Pfeiffer 1990 study was a cross-over trial

Table 9: Impact of the Removal of Studies Judged to be at High or Unclear ROB for Outcome Assessor Blinding on Results.

Intervention	Dichotomies	Analysis including all studies		P Value	Analysis excluding studies at high or unclear ROB		P Value
		N	RR (95% CI)		N	RR (95% CI)	
Allopurinol	Any mucositis	4	0.77 (0.50, 1.19)	0.24	3	0.93 (0.73, 1.20)	0.59
	Moderate to severe[3]	2	0.66 (0.50, 0.86)	0.002	2	0.66 (0.50, 0.86)	0.002
	Severe	2	0.81 (0.63, 1.04)	0.09	2	0.81 (0.63, 1.04)	0.09
Amifostine	Any mucositis	3	0.95 (0.91, 0.99)	0.007	0	-	
	Moderate to severe	6	0.78 (0.62, 0.98)	0.03	1	1.03 (0.83, 1.28)	0.80
	Severe	9	0.68 (0.45, 1.03)	0.07	1	1.76 (1.01, 3.07)	0.05
Antibiotic pastille / paste	Any mucositis	3	0.92 (0.85, 0.99)	0.03	3	0.92 (0.85, 0.99)	0.03
	Moderate to severe	2	0.92 (0.78, 1.08)	0.32	2	0.92 (0.78, 1.08)	0.32
	Severe	3	0.87 (0.71, 1.07)	0.19	3	0.87 (0.71, 1.07)	0.19
Chlorhexidine	Any mucositis	4	0.76 (0.47, 1.24)	0.27	4	0.76 (0.47, 1.24)	0.27
	Moderate to severe	3	0.93 (0.72, 1.21)	0.58	3	0.93 (0.72, 1.21)	0.58
	Severe	4	0.82 (0.54, 1.23)	0.33	3	0.78 (0.44, 1.38)	0.39
G-CSF	Any mucositis	4	0.77 (0.48, 1.23)	0.27	3	0.87 (0.56, 1.35)	0.53
	Severe	2	0.36 (0.15, 0.86)	0.02	2	0.36 (0.15, 0.86)	0.02
Glutamine	Any mucositis	6	0.77 (0.56, 1.05)	0.10	3	0.85 (0.57, 1.26)	0.42
	Moderate to severe	6	0.87 (0.69, 1.10)	0.25	3	0.89 (0.68, 1.16)	0.38
	Severe	8	0.52 (0.29, 0.93)	0.03	4	0.57 (0.23, 1.38)	0.21
Honey	Any mucositis	3	0.70 (0.56, 0.88)	0.002	1	0.37 (0.21, 0.65)	0.0006
	Moderate to severe	2	0.48 (0.31, 0.74)	0.0009	0	-	-
	Severe	2	0.26 (0.13, 0.52)	0.0002	0	-	-
Laser	Any mucositis	3	0.91 (0.71, 1.17)	0.47	2	0.97 (0.63, 1.48)	0.87
	Moderate to severe	2	0.64 (0.38, 1.08)	0.10	1	1.66 (0.52, 5.28)	0.39
	Severe	2	0.20 (0.06, 0.62)	0.006	1	0.74 (0.13, 4.10)	0.73
Radiotherapy (am v pm)	Severe	2	1.07 (0.85, 1.36)	0.56	2	0.59 (0.24, 1.43)	0.24

[3] Interventions which became statistical beneficial after the removal of studies assessed to be at high or unclear ROB are highlighted in green. Interventions which moved from significant to non-significant are highlighted in yellow.

Intervention	Dichotomies	Analysis including all studies		P Value	Analysis excluding studies at high or unclear ROB		P Value
		N	RR (95% CI)		N	RR (95% CI)	
Sucralfate	Any mucositis	4	1.03 (0.96, 1.11)	0.42	4	1.03 (0.96, 1.11)	0.42
	Moderate to severe	5	0.94 (0.67, 1.33)	0.75	5	0.94 (0.67, 1.33)	0.75
	Severe	8	0.74 (0.54, 1.01)	0.06	7	0.83 (0.64, 1.08)	0.17

4.6.2.2.1 Allopurinol

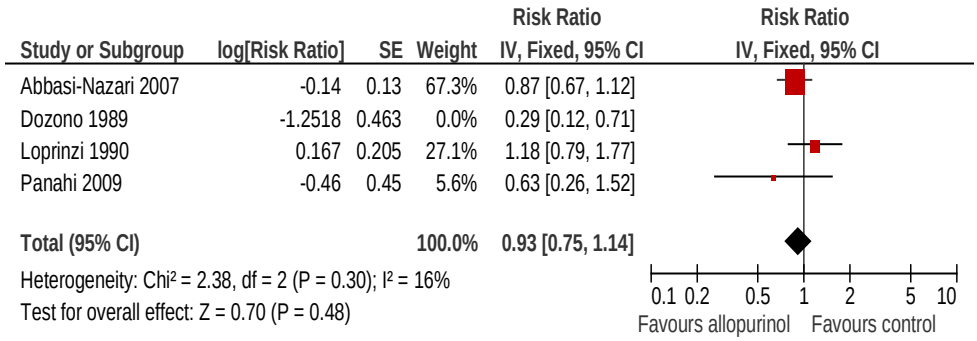


Figure 16: Allopurinol 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding[4]

Three of the four studies included in the allopurinol meta-analyses were described as being double blind and were therefore assessed to be at low risk of bias. The exclusion of the Dozono and colleagues study (1989), altered the risk ratio for the prevention of mild mucositis from 0.77 (95% CI 0.50, 1.19) to 0.93 (95% CI 0.75, 1.14) (Figure 16). As all studies in these analyses were assessed to be at low ROB, the moderate and severe dichotomies remained unchanged.

[4] Generic inverse variance method used as Dozono 1989 and Loprinzi 1990 studies were cross-over trials

4.6.2.2.2 Amifostine

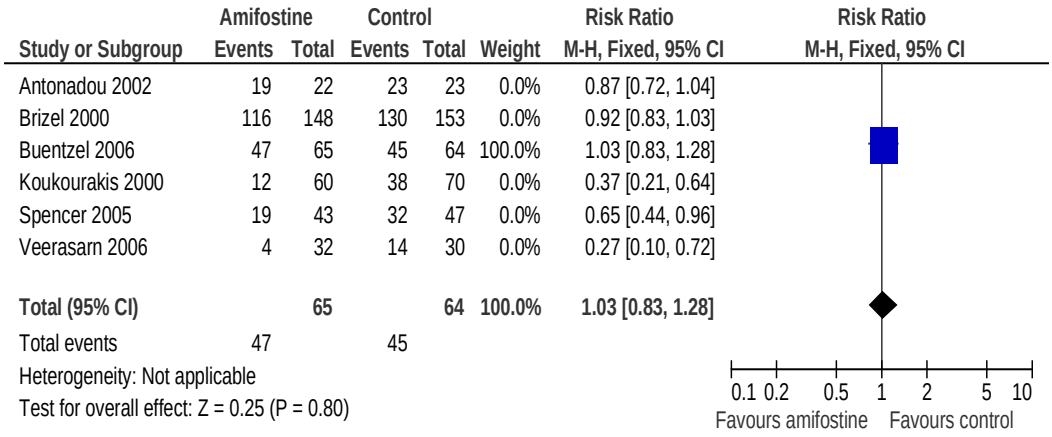


Figure 17: Amifostine: 'Moderate to Severe mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

Only one of the 11 studies included in the amifostine analysis was assessed as being at low ROB for outcome assessment. None of the studies included in the 'any' mucositis dichotomy employed outcome assessor blinding, and this category was therefore removed from the sensitivity analysis. The removal of the other inclusions, altered the risk ratio from 0.78 (95% CI 0.62, 0.98) to 1.03 (95% CI 0.83, 1.28) in the prevention of moderate mucositis dichotomy (Figure 17) and from 0.68 (95% CI 0.45, 1.03) to 1.76 (95% CI 1.01, 3.07) for the prevention of severe mucositis (Figure 18). In this latter analysis, the results were changed to significantly favour the control (P=0.05).

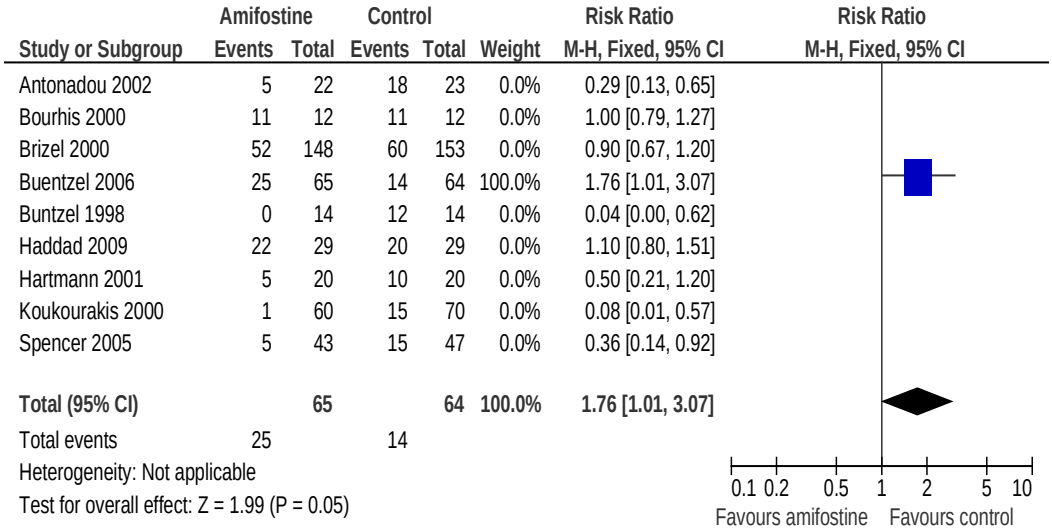


Figure 18: Amifostine 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

4.6.2.2.3 Chlorhexidine

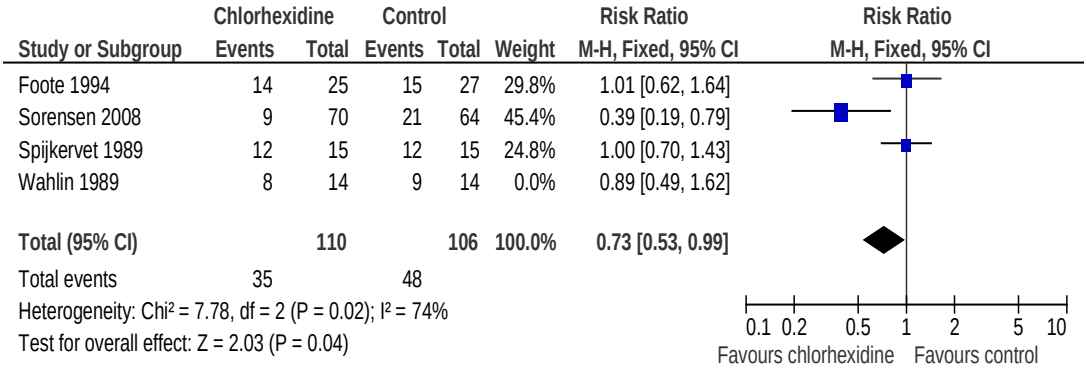


Figure 19: Chlorhexidine 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

Seven of the eight studies included in the chlorhexidine meta-analyses were deemed to be at low ROB for outcome assessor blinding. The removal of the Wahlin study (1989), which did not employ blinding, significantly altered the risk ratio for the severe mucositis analysis from 0.82 (95% CI 0.54, 1.23) to 0.73 (95% CI 0.53, 0.99) (P=0.04) (Figure 19). The results for mild and moderate mucositis were unchanged as all studies in these dichotomies were assessed at low ROB for outcome assessor blinding.

4.6.2.2.4 G-CSF

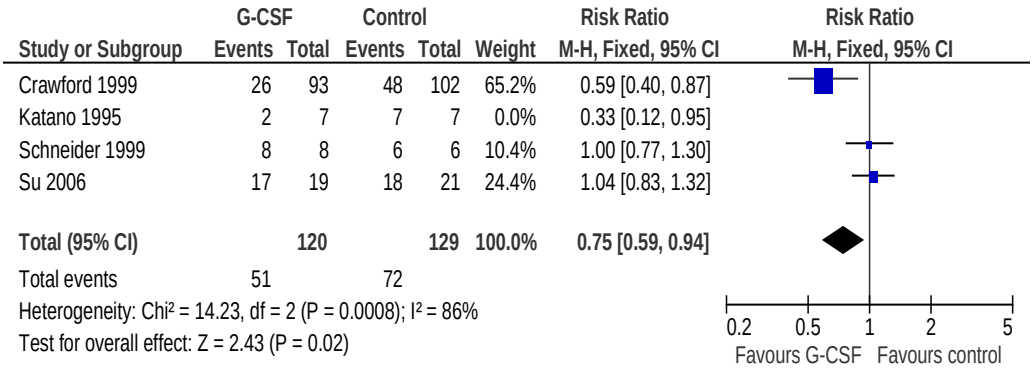


Figure 20: G-CSF 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

Three of the studies included in the G-CSF analyses were assessed as being at low ROB for outcome assessor blinding. The exclusion of the Katano study (1995), which employed no blinding, altered the risk ratio to significantly favour G-CSF for the prevention of 'any' mucositis: from 0.77 (95% CI 0.48, 1.23) to 0.75 (95% 0.59, 0.94) (P=0.02) (Figure 20). The results of the moderate and severe mucositis analyses remained the same.

4.6.2.2.5 Glutamine

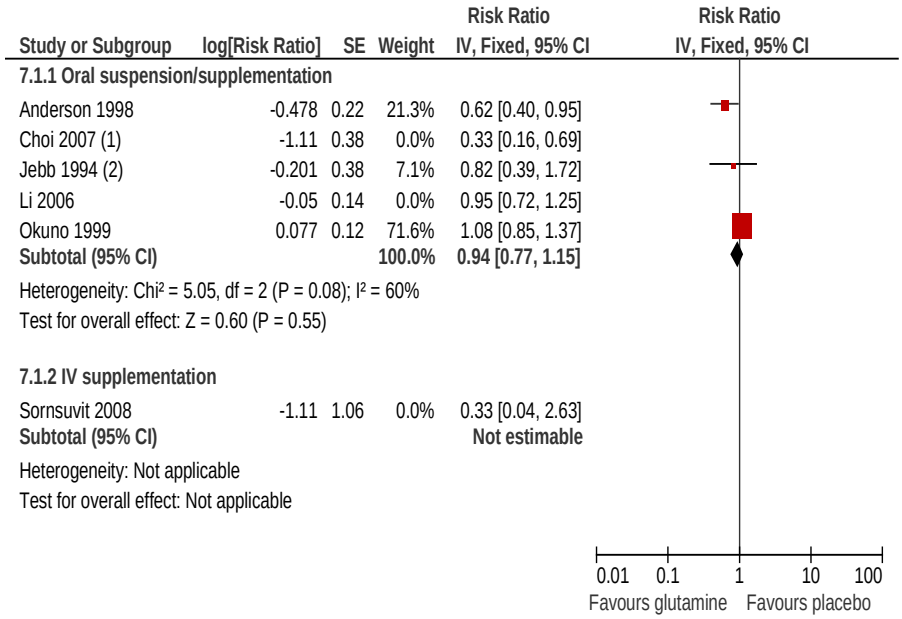


Figure 21: Glutamine 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding[5]

Five of the ten studies included in the glutamine analysis were assessed as being at low ROB for outcome assessment. The removal studies which did not employ blinding altered the risk ratio from 0.77 (95% CI 0.56, 1.05) to 0.94 (95% CI 0.77, 1.15) for the 'any mucositis' dichotomy (Figure 21); from 0.87 (95% CI 0.69, 1.10) to 0.89 (95% CI 0.69, 1.16) in the 'moderate to severe' dichotomy (Figure 22) and from 0.52 (95% CI 0.29, 0.93) to 0.57 (0.23, 1.38) in the severe mucositis dichotomy (Figure 23).

[5] Generic inverse variance method used as Anderson 1998 and Jebb 1994 studies were cross-over trials

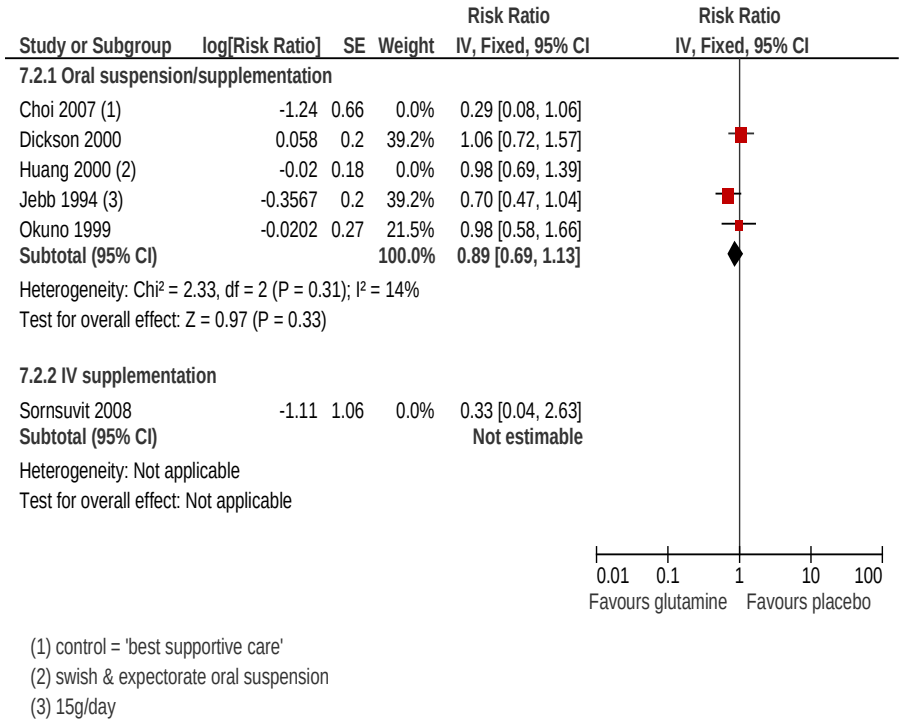


Figure 22: Glutamine 'Moderate to Severe mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding[6]

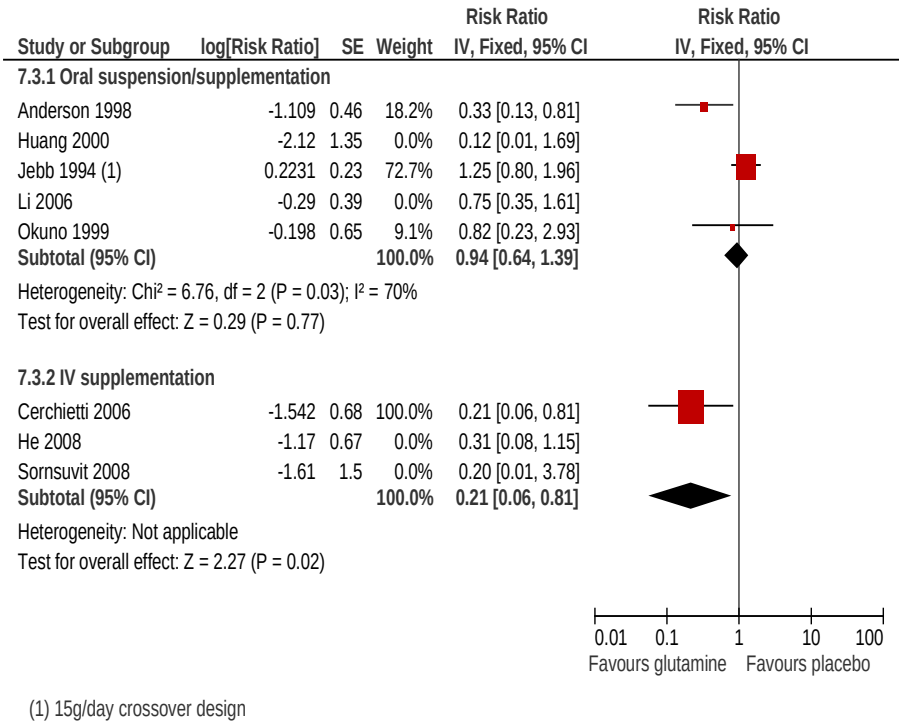


Figure 23: Glutamine 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding[7]

[6] Generic inverse variance method used as Jebb 1994 study was a cross-over trial
[7] Generic inverse variance method used as Anderson 1998 and Jebb 1994 studies were cross-over trials

4.6.2.2.6 Honey

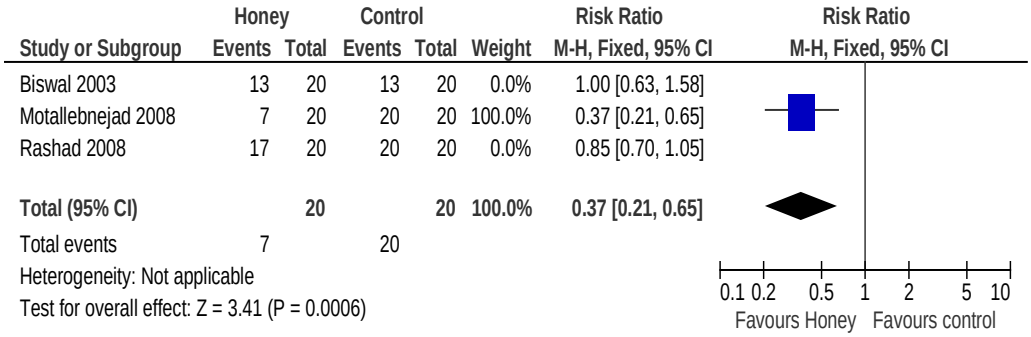


Figure 24: Honey 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

Of the three studies entered into the analysis which investigated honey for the prevention of mucositis, one was assessed as being at low risk of bias for outcome assessor blinding (Motallebnejad et al., 2008). This intervention had been previously found to be beneficial in the prevention of all dichotomies for mucositis, albeit with high levels of heterogeneity in data in the 'any' or 'moderate plus severe mucositis' dichotomies. The removal of studies assessed at high ROB for outcome assessor blinding removed the moderate to severe and severe dichotomies, and altered the risk ratio for 'any mucositis' from 0.70 (95% CI 0.56, 0.88) to 0.37 (95% CI 0.21, 0.65) (Figure 24).

4.6.2.2.7 Laser

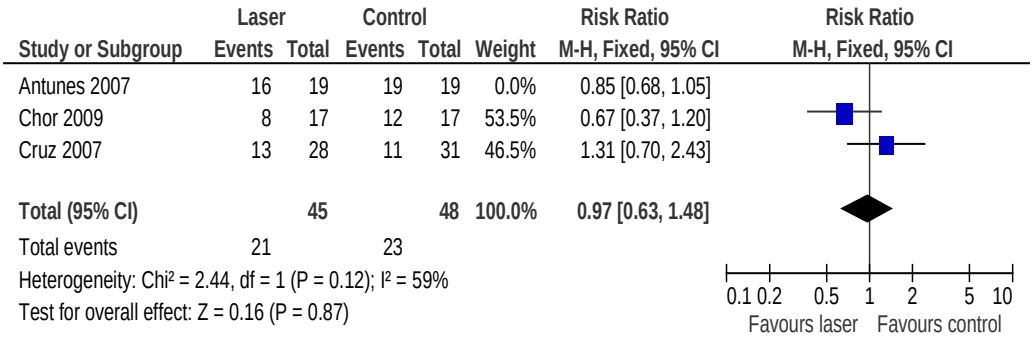


Figure 25: Laser 'Any Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

Five studies of the six studies investigating the use of laser in the prevention of mucositis were assessed to be at low ROB for outcome assessor blinding; however, two of these studies were text only inclusions, which could not be included in the sensitivity analysis (Bensadoun et al., 1999, Schubert et al., 2007) and the other study compared laser application to povidone-iodine and is therefore unchanged (Arun Maiya et al., 2006). The exclusion of the unblinded Antunes and colleagues study (2007), altered the risk ratio from 0.91 (95% 0.71, 1.17) to 0.97 (95% CI 0.63 to 1.48) for the prevention of 'any' mucositis (Figure 25), from 0.64 (95% CI 0.38, 1.08) to 1.66 (95% CI 0.52, 5.28) in the prevention of 'moderate to severe' mucositis (Figure 26) and from 0.20 (95% CI 0.06, 0.62) to 0.74 (95% CI 0.13, 4.10) in the prevention of 'severe' mucositis category (Figure 27).

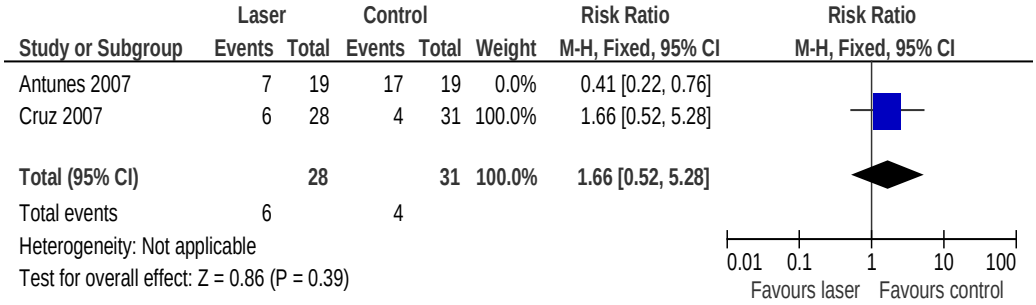


Figure 26: Laser 'Moderate to Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

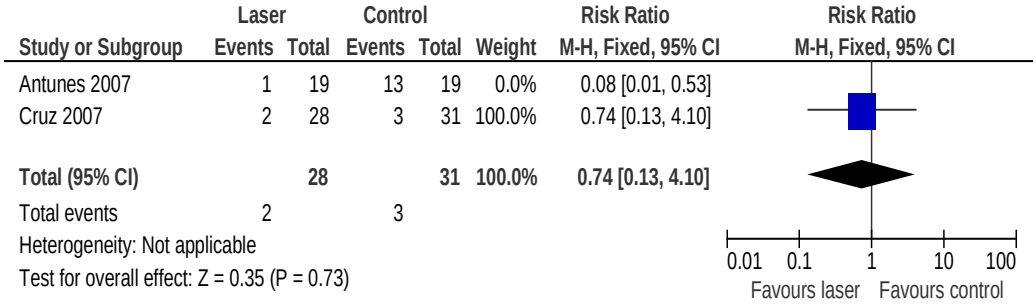


Figure 27: Laser 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

4.6.2.2.8 Radiotherapy am versus pm

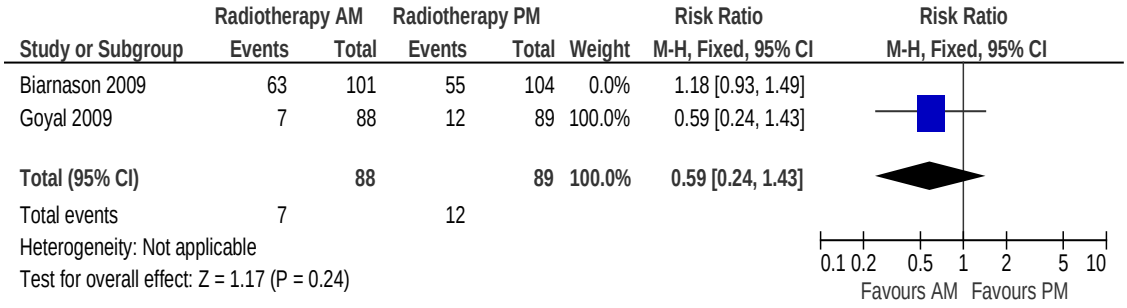


Figure 28: Radiotherapy Morning versus Afternoon 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding

Blinding of outcome assessor was employed in only one of the two studies included in the morning versus evening radiation meta-analysis (Goyal et al., 2009). The exclusion of the unblinded Bjarnason and colleagues study (2009), altered the risk ratio from 1.07 (95% 0.85, 1.36) to 0.59 (95% CI 0.24 to 1.43) for the prevention of 'severe' mucositis (Figure 28).

4.6.2.2.8 Sucralfate

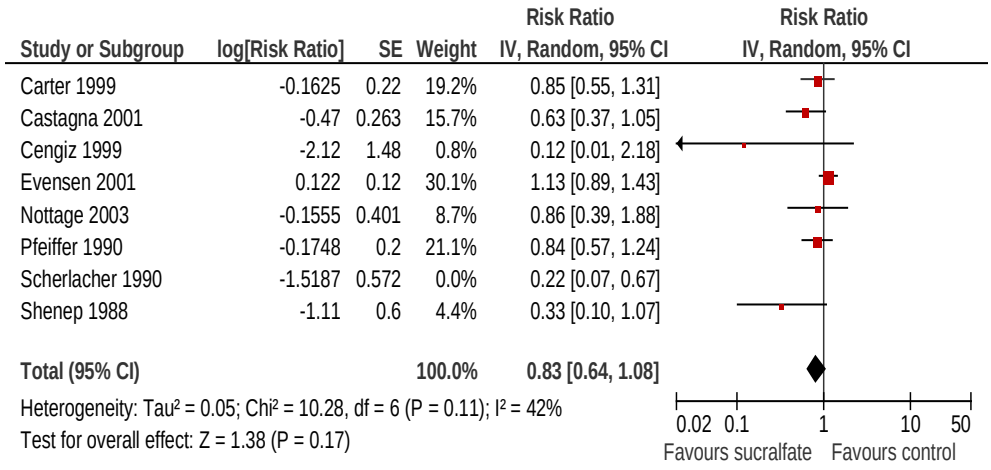


Figure 29: Sucralfate 'Severe Mucositis' Dichotomy After Exclusion of Studies Assessed to be at Unclear or High ROB for Outcome Assessor Blinding[8]

[8] Generic inverse variance method used as Pfeiffer 1990 study was a cross-over trial

Eleven of the 12 studies included in the sucralfate analyses were assessed to be at low risk of bias; however, two of these studies were text only inclusions which could not be included in the sensitivity analysis (Epstein and Wong, 1994, Lievens et al., 1998). The removal of the Scherlacher study (1990), altered the risk ratio for severe mucositis from 0.74 (95% CI 0.54, 1.01) to 0.83 (95% CI 0.64, 1.08) (Figure 29). The generic inverse variance method was used for this analysis as the Pfeiffer and colleagues study (1990), was a cross-over trial. As the Scherlacher study (1990), only provided data for the severe dichotomy, the other results remained unchanged.

4.6.2.3 Overall ROB

Ten studies were assessed at low ROB overall (8%); 82 (63%) were described as unclear; and the remaining 38 studies (29%) were defined as being at high ROB. Two of the studies assessed to be at low risk of bias could not be entered into the sensitivity analysis because they were either a text only inclusion (Madan et al., 2008) or were presented in the single studies table in the main version of the review (Saarilahti, 2002). Therefore the results of eight studies are presented in Table 10. After the exclusion of studies assessed to be at high or unclear ROB, only one intervention, G-CSF, was found to be statistically beneficial for the prevention of severe mucositis. In addition, the results of the moderate to severe dichotomy for chlorhexidine were changed to significantly favour the control group.

Table 10: Impact of the Removal of Studies Judged to be at High or Unclear Overall ROB[9][10]

Intervention	Dichotomies	Analysis including all studies		P Value	Analysis excluding studies at high or unclear ROB		P Value
		N	RR (95% CI)		N	RR (95% CI)	
Allopurinol	Any mucositis	4	0.77 (0.50, 1.19)	0.24	0	-	-
	Moderate to severe	2	0.66 (0.50, 0.86)	0.002	0	-	-
	Severe	2	0.81 (0.63, 1.04)	0.09	0	-	-
Aloe Vera	Severe	2	0.74 (0.58, 0.96)	0.02	0	-	-

[9] Interventions which became statistical beneficial after the removal of studies assessed to be at high or unclear ROB are highlighted in green. Interventions which do not change and remain significant are highlighted in yellow.
[10] Studies found to be statistically beneficial for the prevention of mucositis in the updated full prevention review are highlighted in blue

Intervention	Dichotomies	Analysis including all studies		P Value	Analysis excluding studies at high or unclear ROB		P Value
		N	RR (95% CI)		N	RR (95% CI)	
Amifostine	Any mucositis	3	0.95 (0.91, 0.99)	0.007	0	-	-
	Moderate to severe	6	0.78 (0.62, 0.98)	0.03	0	-	-
	Severe	9	0.68 (0.45, 1.03)	0.07	0	-	-
Antibiotic pastille / paste	Any mucositis	3	0.92 (0.85, 0.99)	0.03	0	-	-
	Moderate to severe	2	0.92 (0.78, 1.08)	0.32	0	-	-
	Severe	3	0.87 (0.71, 1.07)	0.19	1	0.87 (0.70, 1.10)	0.24
Chlorhexidine	Any mucositis	4	0.76 (0.47, 1.24)	0.27	1	1.04 (0.93, 1.15)	0.50
	Moderate to severe	3	0.93 (0.72, 1.21)	0.58	2	1.42 (1.05, 1.93)	0.02
	Severe	4	0.82 (0.54, 1.23)	0.33	1	1.01 (0.62, 1.64)	0.97
Cryotherapy	Any mucositis	5	0.74 (0.57, 0.95)	0.02	0	-	-
	Moderate to severe	5	0.53 (0.31, 0.91)	0.02	0	-	-
	Severe	5	0.36 (0.17, 0.77)	0.008	0	-	-
G-CSF	Any mucositis	4	0.77 (0.48, 1.23)	0.27	2	1.03 (0.86, 1.24)	0.74
	Severe	2	0.36 (0.15, 0.86)	0.02	2	0.36 (0.15, 0.86)	0.02
Glutamine	Any mucositis	6	0.77 (0.56, 1.05)	0.10	0	-	-
	Moderate to severe	6	0.87 (0.69, 1.10)	0.25	0	-	-
	Severe	8	0.52 (0.29, 0.93)	0.03	0	-	-
GM-CSF	Any mucositis	2	0.93 (0.84, 1.04)	0.21	1	0.91 (0.80, 1.04)	0.16
	Moderate to severe	2	0.89 (0.76, 1.05)	0.17	0	-	-
	Severe	6	0.73 (0.51, 1.04)	0.08	2	1.00 (0.60, 1.67)	0.99
Honey	Any mucositis	3	0.70 (0.56, 0.88)	0.002	0	-	-
	Moderate to severe	2	0.48 (0.31, 0.74)	0.0009	0	-	-
	Severe	2	0.26 (0.13, 0.52)	0.0002	0	-	-
Keratinocyte GF	Any mucositis	2	0.82 (0.71, 0.94)	0.005	0	-	-
	Moderate to severe	6	0.80 (0.68, 0.94)	0.006	0	-	-
	Severe	5	0.75 (0.62, 0.89)	0.001	0	-	-
Laser	Any mucositis	3	0.91 (0.71, 1.17)	0.47	0	-	-
	Moderate to severe	2	0.64 (0.38, 1.08)	0.10	0	-	-
	Severe	2	0.20 (0.06, 0.62)	0.006	0	-	-
Pilocarpine	Any mucositis	2	1.05 (1.00, 1.10)	0.06	0	-	-
	Moderate to severe	2	1.05 (0.94, 1.16)	0.41	0	-	-

Intervention	Dichotomies	Analysis including all studies		P Value	Analysis excluding studies at high or unclear ROB		P Value
		N	RR (95% CI)		N	RR (95% CI)	
Povidone - Iodine	Any mucositis	2	0.90 (0.76, 1.08)	0.27	0	-	-
	Moderate to severe	2	0.82 (0.62, 1.10)	0.18	0	-	-
	Severe	2	0.65 (0.40, 1.06)	0.08	0	-	-
Prostaglandin	Any mucositis	3	1.03 (0.94, 1.12)	0.57	0	-	-
	Severe	3	1.01 (0.77, 1.33)	0.93	0	-	-
Radiotherapy (am v pm)	Severe	2	1.07 (0.85, 1.36)	0.56	0	-	-
Sucralfate	Any mucositis	4	1.03 (0.96, 1.11)	0.42	0	-	-
	Moderate to severe	5	0.94 (0.67, 1.33)	0.75	1	0.94 (0.67, 1.33)	0.75
	Severe	8	0.74 (0.54, 1.01)	0.06	1	0.33 (0.10, 1.07)	0.06

4.7 Discussion

In Cochrane reviews, ROB assessments play an important part in how the results of studies are interpreted. As review authors can choose to exclude studies at high risk of bias overall, it may be beneficial for authors planning future studies to think about the risk of bias in their study design if they are aiming for inclusion in a Cochrane meta-analysis.

The results of studies assessed as being at high ROB should be interpreted with caution. Honey and Cryotherapy were found to be significantly beneficial for the prevention of mucositis at all levels of interest in the full review (Worthington et al., 2010). However, none of the cryotherapy studies employed adequate blinding; four were conducted with no blinding, while Mahood and colleagues stated that staff assessing mucositis were often unaware of allocations (Mahood et al., 1991), and was therefore classified as ‘unclear’. In addition, two of the three honey studies employed no blinding, while Motallebnejad used a single blind design in which the outcome assessor was blind (Motallebnejad et al., 2008). Clearly both of these interventions suffer from methodological issues which impact the ROB assessments. It is obviously impossible to blind patients and research staff to whether a patient receives ice chips or not. However, it should possible with careful planning to blind an outcome assessor, especially if patients are being treated as outpatients. Even in small studies, a member of the research team who is not tasked with the daily care of the patients is usually able to fulfil this

role. This has been done successfully in four out of the five laser studies in the review and in one of the two morning versus evening radiation trials, even though the blinding of patients and other personnel was impossible (Arun Maiya et al., 2006, Bjarnason et al., 2009, Cruz et al., 2007).

Adequate allocation concealment should also be possible to achieve. Staff planning to conduct clinical trials in hospital settings commonly have access to a clinical trials unit, which should be able to arrange such central allocation by telephone or fax. If such a service is unavailable, there is still the possibility that the allocation can be concealed using envelopes or drug containers of identical appearance, or through the use of pharmacy controlled randomisation.

In addition to study design, the manner in which studies are written up is also important, as a well-conducted trial with a poorly written paper may be misclassified as being at high or unclear ROB (Nuesch et al., 2009). It is possible that some ROB assessments may change if authors were contacted and asked specific questions about the design and execution of their study. However, attempting to do this in a manner that does not lead or prompt a certain answer is difficult to achieve, as this may introduce other forms of bias into the results. While the manner in which a trial is written up for publication remains important, it is clear that future studies should be designed with ROB in mind.

At present the results of the sensitivity analysis for overall ROB does not appear in the Cochrane prevention review, which may be an oversight. Although, overall risk of bias decisions were discussed alongside each intervention in the results of the review, it is possible that the inclusion of the overall risk of bias sensitivity analysis might provide additional useful information to clinicians. Table 10 shows that the exclusion of studies assessed for unclear or high risk of overall bias changed the results of the moderate to severe dichotomy for chlorhexidine to significantly favour placebo. As chlorhexidine is an intervention which is commonly used in the prevention of oral mucositis (Glenny et al., 2004), despite a lack of benefit being identified in previous updates of the Cochrane prevention review (Worthington et al., 2007), the publication of these findings may help

to alter current clinical practice. The incorporation of such sensitivity analyses should therefore be considered for inclusion in the next update of the review.

The Cochrane method of assessing ROB is a useful method of assessing potential biases in a study, however, these assessments are not without issue. As with any method of assessment, decisions can be subjective and be influenced by the experience of a researcher. The Cochrane handbook (Higgins and Altman, 2009) provides some examples of studies at high, unclear or low risk of bias in each category, however, the researcher found a number of studies which did not clearly fit within any of the criteria. The practice of conducting ROB assessments in duplicate with other members of the Oral Health Group proved invaluable in these circumstances and should be adopted in other reviews. Authors of future reviews need to carefully consider their motives for conducting a sensitivity analysis of their reviews prior to their use, and in addition pre-specify which criteria they consider to be 'key domains', to prevent such analyses becoming a fishing expedition.

4.8 Conclusion

In this chapter studies included in the Cochrane review of interventions for the prevention of mucositis were assessed for ROB (Worthington et al., 2010). The assessment of bias in this manner is important in order to avoid exaggerating the effect estimate of a particular intervention (Nuesch et al., 2009). After consideration of the impact of potential biases the interpretation of study results, the following will be built into the feasibility design:

- A central method of allocation, the hospital pharmacy, will be used to dispatch the intervention and placebo products, therefore ensuring adequate allocation concealment
- Drugs containers which are identical in appearance and sequentially numbered, will also be used to ensure adequate allocation concealment
- Blinding of outcome assessor will be attempted to ensure that mucositis assessments, together will all other data collection, will be conducted without the knowledge of allocations.

Chapter 5: What can we learn from previous studies?

5.1 Introduction

In this chapter the conclusions of the Cochrane review (Worthington et al., 2010) will be analysed to determine what information they can provide to help researchers planning future studies. In addition, some of the studies excluded from the Cochrane review will also be discussed.

5.2 Aim

To review the studies included in the Cochrane review update to determine:

- what the expected rate of recruitment is for future trials
- what other outcomes were reported
- the timing of oral assessment that were used
- the problems and pitfalls that were experienced

5.3 Methods

Studies included in the Cochrane review update were examined to determine if they provided any relevant information. Studies providing dates for recruitment were included in the analysis. If exact dates were not given, data were inputted using the first day of the month for start of recruitment and the last possible day in the month for the end of recruitment. Mean averages were then calculated to provide the average number of patients recruited per week overall. A sub-set analysis was then conducted for single site studies.

5.4 Results

5.4.1 Recruitment

80 of the 130 studies (61.5%) assessed provided enough information to calculate recruitment rates in patient per week. The total number of patients recruited by these studies was 6812. The average number of patients recruited per week was 1.13. The highest recruitment rate recorded in a study was 7.66 patients per week. This was a multi-site study of iseganan in the prevention of mucositis in head and neck cancer patients undergoing a mix of therapies (Trotti et al., 2004). The lowest recruitment rate

recorded meanwhile was 0.153 patients per week, in a study investigating glutamine in patients with solid tumour undergoing chemotherapy (Anderson et al., 1998). As expected, the majority of studies reporting high rates of recruitment were multi-site studies; if such studies were excluded, and the averages recalculated for only the single site studies, the mean average rate of recruitment was reduced to 0.79 patients per week.

5.4.2 Other outcomes

One hundred of the 130 studies assessed mucositis as the primary outcome measure. Twenty-four studies assessed mucositis as a secondary outcome, while in seven studies it was unclear whether mucositis was the primary outcome measure. Figure 30 shows the frequency of the other reported outcome measures and illustrates that there was little consistency in which other outcomes were reported by the assessed studies. It is important to recognise that these outcome measures are what the authors choose to report, and there may have been other outcomes of interest which have not been reported in the publications assessed. However, it is impossible to estimate the scale of any omission without access to the original trial protocols.

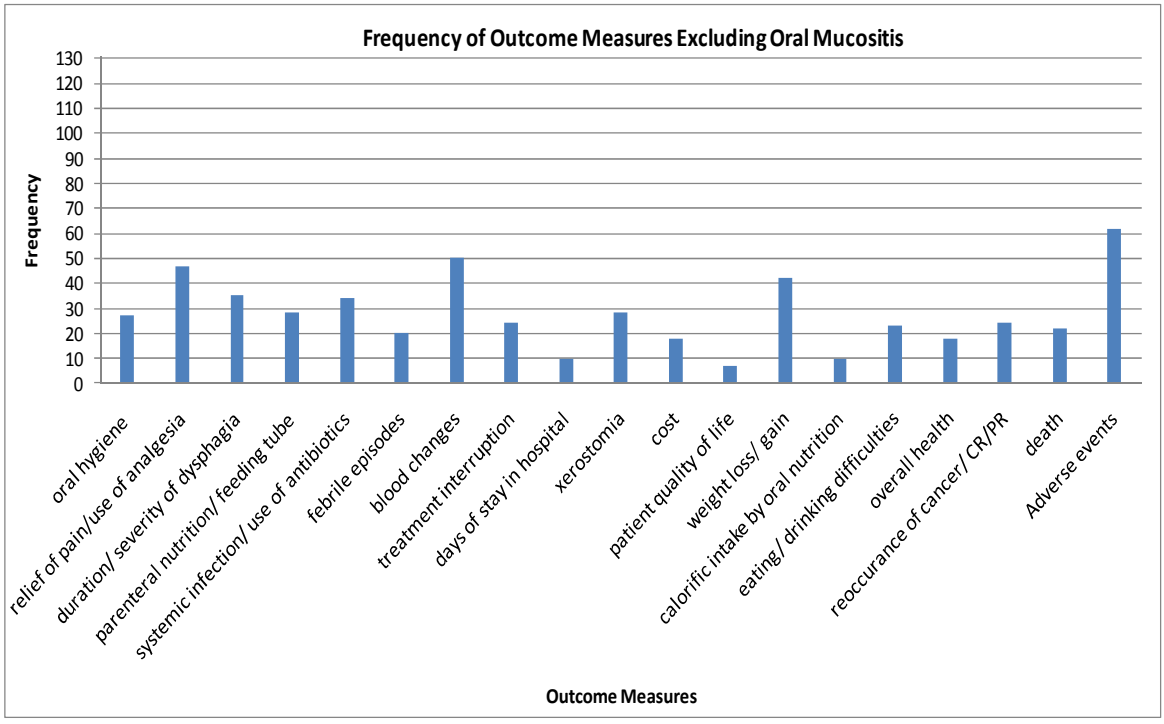


Figure 30: Frequency of Outcome Measures Other Than Mucositis to be Included in the Cochrane Review Update

Adverse events were the most frequently reported outcome measure and were reported by 62 studies (47.6%). Blood changes were reported by 50 studies (38%), while patient reports of pain and use of analgesics were reported by 47 studies (36%). Patient weight loss or gain was the fourth most frequently reported outcome, and was detailed in 42 publications (32%). Dysphagia was reported by 35 studies (27%) and systemic infection or the use of antibiotics by 34 (26%). Oral hygiene, occurrence of febrile episodes, occurrence of death or overall health, xerostomia, cancer reoccurrence, patients difficulties in eating or drinking, calorific intake, the cost of the intervention and length of hospital stay were all outcome measures reported in less than 21% of the studies assessed for ROB. Patient quality of life was the least frequently reported intervention (5%).

5.4.3 Oral assessment

Seventeen studies (13%) provided no information regarding the frequency of assessment, seven of these were translated studies, and this may represent an oversight on the data extraction sheet provided to the translators. Forty seven (35.9%) studies assessed mucositis weekly, 16 (12%) twice weekly and 24 (18%) daily. Three studies (2%) assessed the oral cavity trice weekly, while two studies (1.5%) assessed the oral cavity every two days (Lockhart et al., 2005, Oberbaum et al., 2001). Three studies only assessed the oral cavity twice: in one of these studies assessments were carried out at baseline and day ten (Pfeiffer et al., 1990), in another assessments were conducted at baseline and day 12 (Li et al., 2006), while the third study gave no more information (Sorensen et al., 2008). Three studies assessed the oral cavity three times during data collection (Cruz et al., 2007, Panahi et al., 2010, Pitten et al., 2003). Two studies assessed the oral cavity four times, both these studies were keratinocyte GF studies, and both assessed patients on day one, four, eight and 15 (Meropol et al., 2003, Rosen et al., 2006). Two studies employed monthly assessments (Dodd et al., 1996b, Jebb et al., 1994). Five studies (3.8%) stated that they used ‘historical methods’ to assess mucositis when the patient was seen in clinic some weeks after treatment. However, as no additional information is given for these studies, it is difficult to know what is meant by this statement. It is possible that the authors conducted a review of the patient notes. The remaining seven studies employed variable timescales for assessment. For example, Cartee and colleagues (1995) assessed the oral cavity daily between days one and five, then daily from day eight until ten and then on days 15 and 22. Unfortunately, the

authors give no rationale for the use of such timings. The high number of studies employing weekly assessment may be misleading, as a subset analysis revealed that 43 (91%) of these studies were trials involving head and neck patients undergoing radiotherapy and, or chemoradiotherapy. These patients tend to be treated on an outpatient basis, and are seen in clinic once a week, which may explain the high numbers of studies employing weekly oral assessment.

5.4.4 Problems and pitfalls

Of the 130 studies assessed 12 (9%) studies gave information about the problems they experienced during data collection. Two studies reported more than one problem (Nottage et al., 2003, Veness et al., 2006). Six studies reported problems in recruiting patients into the study (Dorr et al., 2007, Gandemer et al., 2007, McAleese et al., 2006, Su et al., 2004, Su et al., 2006, Veness et al., 2006). While two studies stopped early because of issues with either the intervention or placebo products: Veness and colleagues (2006), reported a difficulty in obtaining study medications in later parts of the trial, despite this trial being sponsored, and the products supplied, by a pharmaceutical company; meanwhile Nottage and colleagues (2003), had to cease recruitment when the expiry date of the placebo was reached. One study ceased recruitment after a change in standard radiotherapy regimes on the unit and the type of radiotherapy used in the study became redundant (Haddad et al., 2009).

Two studies reported drug dispensing errors (Anderson et al., 1998, Trotti et al., 2004). In addition, one study was excluded from the prevention review because of a drug dispensing error (Giles et al., 2003). In the Giles and colleagues study, a drug dispensing error affected 102 patients. These patients were allocated at least one bottle of either intervention or placebo against their randomised assignment. Unfortunately, as the drugs were dispensed every five days, the longer a patient remained on the study, the greater the chances that they were affected by this error. Twenty-seven patients were potentially affected by a problem with a voice activated randomization procedure in the Trotti and colleagues (2004) study. These patients were therefore excluded from the analysis.

5.5: Discussion

This chapter has assessed the literature included in the Cochrane prevention review to determine what information they provide, which could be used to inform future trials. A number of issues have been identified. These will now be discussed.

5.5.1 Feasibility study

Two studies assessed experienced problems during randomisation (Anderson et al., 1998, Trotti et al., 2004). Another study, excluded from the review, reported a pharmacy dispensing error which affected 32% of all patients recruited into the study (Giles et al., 2003). All three of these issues were due to technology failure. It is possible that such issue could have identified if a rigorous feasibility study had been conducted prior to the commencement of data collection. Any technology, pharmacy release procedures, recruitment policies or methods of assessment due to be employed in a trial should be trialled in a feasibility study and the results analysed before the main trail is conducted (Easterbrook and Matthews, 1992). In this way, costly mistakes, such as those experienced in the Giles and colleagues study could be avoided if one element of the study is found not to work.

5.5.2 Recruitment

Recruitment problems were explicitly mentioned by six studies assessed for ROB. However, it could be surmised from the long recruitment periods and the low number of patients recruited that some other studies also experienced problems, but that these authors choose not to discuss these issues in their publications. McAleese and colleagues (2006), for example, recruited 29 patients in 165 weeks, while Anderson and colleagues (1998) recruited 24 patients in 156 weeks. Neither article mentions problems with recruitment. A wide variation in recruitment rates was identified within the literature, with rates of recruitment being much higher in multi-site studies. However, in such multi-site studies research nurses are generally tasked with data collection and recruitment of patients, and as these staff typically work on more than one study at a time, it is possible that recruitment for one particular project may take preference over another. Gandemer and colleagues (2007), stated that nursing staff found it difficult to devote time to the study. However, it is possible that such barriers to recruitment, at least in terms of researchers, could be reduced if a member of staff was employed to

work purely on the study, and take responsibility for conducting all recruitment and data collection. Based on the studies included in the Cochrane review, future multi-site studies can expect to recruit approximately 1.13 patients per week. Single site studies can expect to recruit approximately 0.79 patients a week.

Recruitment into clinical trials is an acknowledged problem in the literature (Gul and Ali, 2010, Toerien et al., 2009). Under recruitment of patients into a trial reduces statistical power and can lead to type II errors, false negatives, if a study fails to recruit the number of patients demanded by the sample size calculation (Gul and Ali, 2010, Oude Rengerink et al., 2010). Slow recruitment into studies also has economic consequences for the trial, as the recruitment period may have to be extended in order to reach targets, which may have considerable consequences in terms of staff and resource utilisation (Gul and Ali, 2010). Many different barriers to patients taking part in research have been identified, which include: a dislike or distrust of the research process, a preference for one intervention in the trial over another, a dislike of the prospect of randomisation or the possibility of being randomised to a placebo arm, and a concern about the possibility of adverse events (Mills et al., 2006, Oude Rengerink et al., 2010). Unfortunately, attempts to address some of these barriers by educating patients about the research process have not been found to significantly increase rates of patient consent (Du et al., 2008, Ellis et al., 2002). The use of a pilot or feasibility study can help identify problems recruiting patients to take part in a study prior to a costlier larger study being conducted.

5.5.3Timing of oral assessments

No consistency was identified regarding the timings of oral assessments in the studies assessed for ROB. Weekly assessments were employed most frequently; however, this result may be confounded by the number of these studies which were conducted in radiotherapy patients, who would commonly be seen for weekly outpatients' appointments. The number of studies which employed historical methods of assessment is concerning as mucositis has been found to be under documented in chart reviews (Dodd et al., 1996a). There is a danger that important oral changes may be missed if oral assessments are conducted too infrequently, however, conversely conducting such assessments too frequently increases the burden on both patients and researchers (Eilers

and Epstein, 2004). The task therefore is to conduct oral assessments frequently enough to detect important changes, but not too frequently as to bother patients. Research has suggested that oral cavity changes can be identified within four hours of the initiation of stressors, in the absence of interventions which act to counteract such a stressor (DeWalt and Haines, 1969). Clearly, conducting oral assessments every four hours is not practical. However, daily assessments of the oral cavity may be feasible.

5.5.4 Adverse event reporting

Fewer than 50% of the articles assessed for ROB reported adverse events. This is a concerning oversight, as this is crucial information when developing future trials of any intervention, and is used to inform risk-benefit analyses. Few studies provided information about how this adverse event reporting was conducted, or provided information regarding how long patients were followed-up after receiving their last dose of intervention or placebo. In those studies which did provide this information, patients were routinely followed up for between 28 and 30 days after their last dose. A length of follow-up of 30 days after a patient receives their last dose of intervention or placebo therefore appears to be appropriate for use in future studies.

5.6 Conclusion

This chapter has assessed studies included in the Cochrane prevention review (Worthington et al., 2010) to determine what information they provide which could be used to inform a future trial. Expected recruitment rates were calculated from papers providing the necessary information. A lack of consistency was identified in the other outcomes reported by these studies. Adverse events were the most frequently reported outcome; however these were reported by only 62 studies (47.6%), a concerning result which should be addressed in future trials. Patient quality of life was the least frequently reported outcome, this supports one of the conclusions in the literature review of this thesis, which stated that patient reports of mucositis were an under-reported area of research. A variety of timings of oral assessment were identified, three studies only assessed the oral cavity twice, which is not appropriate for use in future trials because of the possibility that important changes may be missed. Twelve of the assessed studies reported problems during data collection, which ranged from early stopping due to issues with the intervention or placebo products, to recruitment problems. Three studies

reported drug dispensing errors, which may have been identified prior to starting data collection had a feasibility study been conducted. The next chapter of this thesis will identify appropriate oral assessments for use in a feasibility trial.

Chapter 6 A Systematic Review of Oral Assessment Instruments for Use in Adults

6.1 Rationale

Oral assessment is crucial to accurately monitor and document the severity and progression of mucositis. Accurate assessment using a valid, reliable and sensitive tool, which is easy for the researcher to use, and does not fatigue or increase patient pain is important for both research and clinical settings (Tomlinson et al., 2007). In the clinical setting, regular monitoring of the oral cavity facilitates the employment of interventions for OM treatment and the alleviation of associated symptoms. Within the context of a RCT, accurate oral assessment using a valid, reliable and sensitive tool, which is easy for the researcher to use, and does not fatigue or increase patient pain, is vital for the comparison of intervention and control groups. To identify the various methods of oral assessment currently available in the literature, and to determine the most appropriate instrument available for use in children, the Children's Cancer and Leukaemia Group (CCLG) mouth care group conducted a search of the literature in 2004, and published a systematic review of instruments as part of their mouthcare guidelines in 2006 (UKCCLG-PONF, 2006). The CCLG mouth care group is a multidisciplinary group of experts in the fields of paediatric oncology, evidence based practice and oral care. The primary aim of this group is the development of oral care guidelines for children and young people undergoing therapy for cancer (UKCCLG-PONF, 2006). In early 2008, before the update of the mouthcare guidelines, the literature search was repeated by the author, and the review updated. This systematic review was also reproduced as a linked publication, which was co-authored by the author (Gibson et al., 2010). The results of the 2008 literature search were used by the author to conduct a separate systematic review to determine the most suitable oral assessment instruments for use in a clinical trial of adults with haematological cancers undergoing stem cell transplantation. This systematic review is presented in the remainder of this chapter.

6.2 Objectives

To identify oral assessment instruments previously used for the assessment of oral mucositis in adults in order to select suitable instruments for use in a trial involving patients undergoing stem cell transplantation.

6.3 Method

6.3.1 Eligibility criteria

Articles describing an oral assessment instrument for use in adult patients with cancer receiving treatment, or any study describing either an adaptation of an existing oral assessment instrument, or the validation of an existing instrument.

6.3.2 Information sources and search

In March 2008, the search strategy previously employed when developing the oral care guidelines (UKCCLG-PONF, 2006) was re-run on the following electronic databases: MEDLINE (OVID BIOMED 1980- March 2008), EMBASE (OVID BIOMED1980- March 2008), The Cochrane Library (Issue 2, 2008) and CINAHL (OVID BIOMED1980- March 2008). Briefly, this search strategy was comprised of a root search of terms including 'neoplasm', 'radiotherapy', 'chemotherapy' and 'bone marrow transplantation' and then an oral assessment specific search, which included terms such as 'oral ulcer', 'stomatitis' and 'severity of illness index'. A copy of the complete search strategy can be found in Appendix 2.

6.3.3 Study selection and data collection process

6.3.3.1 Screening, identification of eligible publications and data extraction used for the CCLG guideline update and linked publication

The titles and abstracts of the 2008 search results were first screened by the author and then distributed to another member of the group for duplicate screening. After potentially eligible studies had been identified, the full papers were acquired by the author who then distributed them between paired members of the CCLG mouth care group for extraction in duplicate. Data extraction comprised two distinct phases: the first phase was the extraction of the components of each assessment instrument and the completion of a table showing the frequency of items used to score the oral cavity; the second phase was to determine whether any validity/reliability information was provided in the paper, and if this was present, to assess these studies using an adaptation of the diagnostic studies checklist (Scottish Intercollegiate Guidelines Network (SIGN), 2002). Disagreements between paired members were taken to a third party.

6.3.3.2 Screening, identification of eligible publications and data extraction used for this review

The author then re-read the articles and extracted each of the instruments into the formats shown in Table 11 and Table 12. Articles not meeting the inclusion criteria for the adult review were excluded.

6.3.4 Synthesis of results

Data pooling was narrative in both the CCLG guidelines and linked publication and in this review.

6.4 Results

6.4.1 Study selection

A total of 391 articles were identified during the repeat of the search. Three-hundred and twenty-three of these publications were excluded because either the participants or instrument didn't fulfil the inclusion criteria. The additional 37 publications previously included in the review were also removed. This left 31 potentially eligible publications studies, which was reduced to 28 studies after the removal of a quality of life scale and two duplicate assessment instruments. Fifty-four assessment instruments were identified for inclusion in the CCLG guidelines and linked publication (Gibson et al., 2010). However, four of these instruments were designed, or amended, for use in children (Chen et al., 2004, Gandemer et al., 2007, Gibson et al., 2006, Sung et al., 2006), and as these did not meet the inclusion criteria for this review, these articles were therefore excluded. Therefore 50 oral assessment instruments were identified for inclusion in this review. Figure 31 shows the flow of information through the different phases of the systematic review.

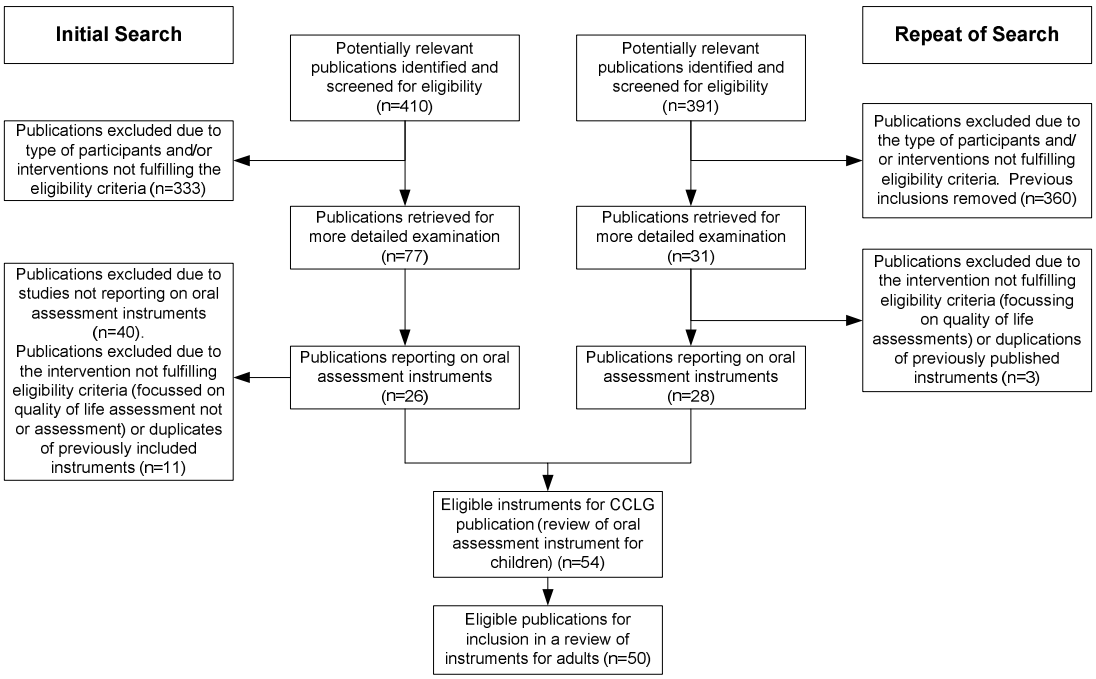


Figure 31: Flow of information through the different phases of the systematic review

(adapted from Gibson et al., 2010, permission granted)

6.4.2 Study characteristics

As suggested by Parulekar and colleagues (1998), these 50 oral assessment instruments can be separated into two groups depending on how they grade the oral cavity (Parulekar et al., 1998). Twenty-one of these instruments identified in the search were "simple scales" which assign symptoms a score collectively using a scale of four or five grades. The remaining 29 scales were "multi-component" scales, which assign a numerical grade to individual oral symptoms (Table 11). Information about inter-rater or intra-rater reliability and validity testing were provided by 12 instruments, 11 of these were multi-component instruments (Dibble, 1996, Donnelly, 1992, Eilers et al., 1988, Kushner et al., 2008, McGuire et al., 2002, Olson et al., 2004, Potting et al., 2006, Sonis et al., 1999, Spijkervet et al., 1989a, Stiff et al., 2006, Tardieu et al., 1996), and one of which was a simple scale (Anonymous, 1991).

Seven of these instruments were validated in patients undergoing autologous or allogeneic transplantation (Donnelly, 1992, Eilers et al., 1988, Kushner et al., 2008, McGuire et al., 2002, Potting et al., 2006, Stiff et al., 2006, Tardieu et al., 1996). Two were validated in radiotherapy patients (Dibble, 1996, Spijkervet et al., 1989a). One in a

mixed group of patients receiving radiotherapy or chemoradiotherapy (Olson et al., 2004). One instrument was validated in chemotherapy patients (Anonymous, 1991), and one in both chemotherapy and radiotherapy patients (Sonis et al., 1999). The number of patients assessed during validation ranged from 10 (Dibble, 1996) to 212 (Stiff et al., 2006).

Ten of the instruments shown in Table 11 and Table 12 were modifications of previous instruments (Aquino et al., 2005, Bolwell et al., 2002, Dudjak, 1987, Ferretti et al., 1988, Hickey et al., 1982, Kushner et al., 2008, McGuire et al., 2002, Olson et al., 2004, Trotti et al., 2000), however, only two of these instruments were re-validated after modifications were made (McGuire et al., 2002, Olson et al., 2004).

Of the 21 simple instruments presented in Table 11, six graded mucositis on a scale from zero to three (Anonymous, 1991, Carl and Emrich, 1991, Ferretti et al., 1988, Hickey et al., 1982, Lindquist et al., 1978, Tanner et al., 1981), 12 used a grading scale numbered between zero and four (Byfield et al., 1985, Chapko et al., 1991, Cox, 1995, Damon et al., 2004, Pitten et al., 2003, Seto et al., 1985, Turhal et al., 2000, Trotti et al., 2000, Van der Schueren et al., 1983, World Health Organization (WHO), 1979), and the remaining three instruments employed a zero to five grading scale (Cancer Therapy Evaluation Program, 2003, Cancer Therapy Evaluation Program, 2009). In all three of these scales, grade five is simply stated as “death”. Five simple scales graded mucositis based on size of confluence or ulceration (Carl and Emrich, 1991, Damon et al., 2004, Ferretti et al., 1988, Trotti et al., 2000, Van der Schueren et al., 1983). However, two of these instruments only used size as a descriptor in the later grades of the instrument and employed other descriptors in the earlier grades (Damon et al., 2004, Van der Schueren et al., 1983).

The 29 multi-component instruments shown in Table 12 varied considerably in their size and complexity. The instrument with the greatest number of categories was the Oral Mucositis Index (OMI), which was comprised of 34 items. This instrument was later modified, and the number of items reduced to 20, by McGuire and colleagues (2002). However, this 20-item OMI still had the second greatest number of categories of all the

instruments included in Table 12. This instrument was the only one to include a set of complex grading instructions for use when determining a grade. The multi-component instrument with the least number of categories was Lievens' oral assessment instrument, which was comprised of two categories: dysphagia and mucositis (Lievens et al., 1998).

Twenty-one of the multi-component instruments shown in Table 12 employed a combined final score. The remaining eight instruments either provided a score for each category or the authors gave insufficient information about whether, or not, a total score was generated when using the scale. Three of the instruments in Table 12 required calculations which were more complex than simple addition or subtraction to determine a final score: Spijkervet and colleagues (1989a), present an instrument for mucositis assessment that grades eight sites in the oral cavity for the presence of mucositis (erythema and ulceration) and the size of these areas. To determine a mucositis grade using this instrument, the degree of mucositis at each of the eight sites was first calculated, and then the scores of the eight sites summed. The final score was calculated by dividing the sum of the sites with mucositis by the number of sites assessed to produce a mean score for the oral cavity (Spijkervet et al., 1989a). The authors provided a summary of this calculation in an equation. The OMAS instrument (Sonis et al., 1999), assessed nine sites of the oral cavity for presence of erythema using a 3-point scale, and size of ulceration, using a four point scale. A total score was generated for this instrument by summing the scores for ulceration and erythema for each site, and then by determining an overall mean score for all nine sites. Bolwell and colleagues (2002) presented a modified OMAS scale which assessed eight sites of the oral cavity. Ulceration was scored either zero (not present) or one (present) and erythema was scored between zero and one (0=none, 0.5=mild to moderate, 1=severe). The total score for this instrument was calculated by summing the ulceration and erythema scores and dividing these scores by the number of evaluable sites, before summing the average ulceration and erythema scores.

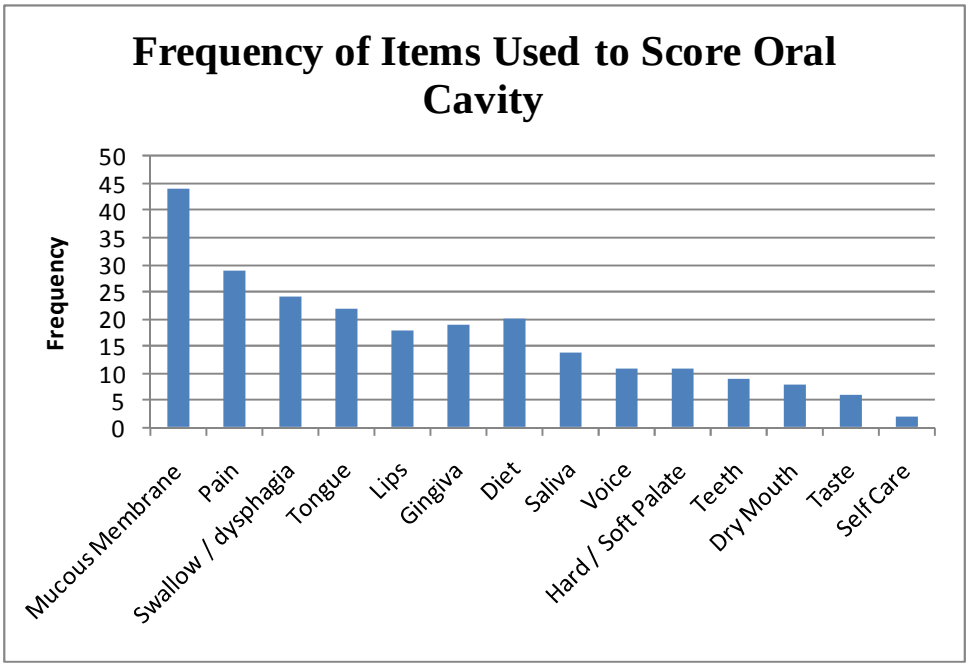


Figure 32: Frequency of Items Used to Score the Oral Cavity

Figure 32 shows the frequency of the various items used to grade mucositis in the instruments shown in Table 11 and Table 12. There seems to be little consistency in which items are commonly included in assessment tools. Not surprisingly, the mucous membrane was the most frequently included in assessment instruments, with 44 instruments (88.8%) including this category. Pain was the second most frequent item, used by 29 instruments (58%). Only 24 (48%) of the assessment instruments identified measured a patient's ability to swallow or level of dysphagia, and the tongue was only scored by 22 instruments (44%). Teeth were included in 9 instruments (18%) and the ability of the patient to perform self-care in only two (4%).

Table 11: Simple Scales

Name	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Other information
Byfield et al, 1985[11]	N/A	"Minimal dysphagia, thinning but no overt break in mucosal integrity"	"Significant dysphasia, semi soft foods only, focal mucosal vesicles or denuded patches"	" Fluids only tolerated by mouth, obvious large confluent patches of mucosal denudation"	"Parenteral fluids only, severe confluent mucosal denudation with bleeding"	Part of a much greater tool, which also includes CNS, lower GI, upper GI, and haematological scoring systems."
Carl et al, 1991[12]	"No clinically noticeable changes"	(Mild) "Colour changes (erythema), no surface ulceration, mild discomfort"	(Moderate) "Surface ulcerations in islands <1 cm, moderate discomfort, able to eat"	(Severe) "Confluent areas of ulceration, tongue, palate, floor of the mouth, buccal mucosa; able to eat with great difficulty only"	N/A	
CALGB (Turhal et al, 2000)[13]	"None"	"Painless ulcers, erythema and mild soreness"	"Painful erythema, edema, or ulcers, but can eat"	"Painful erythema, edema, or ulcers, and cannot eat"	"Requires parenteral or enteral support"	-
Chapko et al, 1989[14]	"None"	"Mild"	"Moderate"	"Severe"	"Life threatening"	-
CTC AE v2 (Radiation)[15], Trotti et al, 2000	"None"	"Erythema of the mucosa"	"Patchy pseudomembranous reaction (patches generally <1.5 cm in diameter and non-contiguous)"	"Confluent pseudomembranous reaction (contiguous patches generally >1.5cm in diameter)"	"Necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion"	Update of Cox et al 1995.

[11] Byfield et al, 1985, p792
[12] Carl et al, 1999, p366
[13] Turhal et al, 2000, p56
[14] Chapko et al, 1989, p181
[15] Trotti et al, 2000, p30

Name		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Other information
CTC AE v2[16] (Chemotherapy), Trotti et al, 2000		"None"	"Painless ulcers, erythema, or mild soreness in the absence of lesions"	"Painful erythema, edema or ulcers but can swallow"	"Painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral (or enteral) nutritional support"	"Severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia".	Update of Cox et al 1995.
CTC AE version 3	**CTC AE v.3**[17] (clinical exam)	"None"	"Erythema of the mucosa"	"Patchy ulcerations or Pseudomembranes"	"Confluent ulcerations or pseudomembranes; bleeding with minor trauma"	"Tissue necrosis significant spontaneous bleeding; life-threatening consequences"	Grade 5= "death"
	CTC AE v.3[18] (functional / symptomatic)	"None"	"Minimal symptoms, normal diet"	"Upper aerodigestive tract sites: Symptomatic but can eat and swallow modified diet."	"Upper aerodigestive tract sites: Symptomatic and unable to adequately aliment or hydrate orally."	"Symptoms associated with life-threatening consequences"	Grade 5= "death"
CTC AE v.4[19]		"None"	"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"	Grade 5= "death"
Damon et al, 2004[20]		"None"	"Erythema"	"Pain requiring continuous narcotics or preventing eating"	"Ulceration>25% oral surface"	"Airway compromise requiring intubation"	

[16] Trotti et al, 2000, p31
[17] CTC AE, 2003, p24
[18] CTC AE, 2003, p24
[19] CTC AE, 2009, p46
[20] Damon et al, 2004, p470

Name	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Other information
Ferretti et al, 1988[21]	"None"	"Mild: Mucosal redness with one or two small ulcerations (<1 cm) and minimal discomfort"	"Moderate: Mucosal ulcerations with one or two large ulcerations (>1cm), substantial discomfort but patient able to eat"	"Severe: Multiple mucosal ulcerations with severe discomfort; patient unable to eat"	N/A	Assessment tool modified from Lindquist (1978) and Tanner (1981).
Hickey et al, 1982[22]	"No Stomatitis"	"Whiteish gingival area observed, or patient mentions slight burning sensation or pain in the oral cavity"	"Moderate erythema and ulcerations or white patches present; patients complains of pain, but can eat, drink or swallow"	"Severe erythema and ulceration or white patches present; patient complains of severe pain and cannot eat, drink or swallow"	N/A	Lindquist/ Hickey scoring tools used interchangeably in many studies. Modification of Lindquist (1978) to include swallow.
Lindquist et al, 1978[23]	"No stomatitis"	"Erythema observable and / or patient mentions slight burning sensation in oral cavity"	"Erythema and ulceration or white patches present upon clinical examination. Patient complains of intra-oral pain but is able to eat"	"Erythema and ulceration or white patches present. Patient complains of severe intra-oral pain and is unable to eat"	N/A	Lindquist/ Hickey scoring tools used interchangeably in many studies.
NIH CTC, 1993[24]	"None"	"Painless ulcers, erythema or mild soreness"	"Painful erythema, oedema, or ulcers, can eat"	"Painful erythema, oedema, or ulcers, cannot eat"	"Require parenteral or enteral support"	
Pitten et al 2003[25]	"No signs / symptoms"	"Reddening, incipient erosions, minimal discomfort"	"Reddening, erosions, small ulcerations, substantial discomfort: patient unable to eat"	"Erosions, ulcerations, severe discomfort: Patient can drink only"	"Severe ulcerations: patient needs parenteral nutrition"	

[21] Ferretti et al, 1988, p485
[22] Hickey et al, 1982, p190
[23] Lindquist et al, 1978, p 313
[24] NIH CTC, 1993
[25] Pitten et al, 2003, p285

Name	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Other information
RTOG/ EORTC, (Acute radiation morbidity) Cox et al, 1995[26]	"No change over baseline"	"Injection/may experience mild pain not requiring analgesic"	"Patchy mucositis that may produce an inflammatory serosanguinous discharge/ may experience moderate pain requiring analgesia"	"Confluent fibrinous mucositis/ may include severe pain requiring narcotic"	"Ulceration, haemorrhage or necrosis"	
Seto et al, 1985[27]	-	"Localized erythema only, with no pain"	"Generalized erythema without pain or localized erythema or ulcers with mild pain"	"Multiple ulcers or generalized erythema with moderate pain"	"Generalized erythema or ulcers with moderate to severe pain"	
Tanner et al, 1981[28]	"None"	"Mucosal redness with minimal discomfort"	"Mucosal redness with some mucosal ulceration and substantial discomfort"	"Mucosal redness, extensive areas of ulceration, much discomfort and dysphasia, necessitating delay of radiotherapy / sometimes of chemotherapy"	N/A	
Van der Schueren et al, 1983[29]	"No changes"	"Slight erythema"	"Pronounced erythema"	"Spotted mucositis"	"Confluent mucositis (patches larger than 0.5cm in diameter)."	

[26] Cox et al, 1995, p1344
[27] Seto et al, 1985, p494
[28] Tanner et al, 1981, p768
[29] Van der Schueren et al, 1983, p200

Name	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Other information
WCCNR, Anon 1991[30]	"The mouth appears healthy. The colour is normal pink. There are no lesions. There is no bleeding. The mucosa is moist. There is no edema or infection present. There are no oral limitations to eating or drinking. The patient experiences no oral discomfort."	"The mouth has evidence of slightly increased redness in one or more areas. There are 1 to 4 lesions somewhere in the oral cavity. The mucosa may appear to be thinning in several areas. There is no bleeding or infection present. The mucosa is moist. There is mild edema in one to several areas. The patient tends to avoid harsh, hot, or spicy foods because the mouth is sensitive to such irritation. The patient experiences mild discomfort that may be described as burning sensation."	"There is moderate increase in redness throughout most of the mucosal surfaces. There are more than 4 lesions somewhere in oral cavity, but they still discretely separate and not coalescing with adjacent lesions. The mucosa tends to bleed upon probing or manipulating. The mucosa appears slightly drier than normal. The saliva may be slightly thicker than normal. Most areas are moderately edematous. There may be evidence suggesting that infections present in the mouth manifested by white or yellow patches. The patient is unable to eat except for very bland soft foods, but is able to drink liquids that are not hot, spicy or acidic. The patient experiences moderate continual pain and requires intermittent analgesics."	"The oral mucosa is severely red throughout all of the oral cavity. There are multiple confluent ulcers which may be to the point of total denudation of the oral cavity. Bleeding is occurring spontaneously without any particular stimulation. There is marked xerostomia. Edema is severe throughout the entire mouth. There are white, yellow, or purulent patches present in the mouth suggesting infection. The patient is unable to eat or drink or even to swallow own saliva. With persuasion, the patient may be able to swallow oral medications. The patient has severe constant pain constant pain requiring systemic analgesia."	-	
WHO[31] Anon, 1979	"None"	"Soreness and erythema"	"Ulcers, erythema. Patient can swallow solid diet"	"Ulcers, extensive erythema. Patient cannot swallow solid diet"	"Mucositis to the extent that alimentation is not possible"	

[30] Anon, 1991, p10-11
[31] WHO, 1979

Table 12: Multi-Component Instruments

Author	Components included	Additional information
Aquino et al, 2005	8 items scored from 0 to 2: lips, tongue, hard and soft palate, buccal and labial mucosa, gingival, teeth, patient assessment of pain, saliva production.	Compound score Modified Walsh Instrument
Beck et al, 1979	16 items scored from 1 to 4: lips (texture, colour, moisture), tongue (texture, colour, moisture), mucous membranes (colour, moisture), gingivae (colour, moisture), teeth (shine, debris, dentures) saliva, voice, ability to swallow. Included patient perceptions of oral cavity.	Compound score
Bentzen et al, 2001	4 items scored: mucositis distribution, pain on swallowing and requirement for analgesics all scored from 0 to 3. Dysphagia scored from 0 to 5.	Grade 1 not used when scoring mucositis distribution. Skin grading also included in instrument.
Bolwell et al, 2002	8 sites scored 0 to 1 for ulceration and erythema: labial mucosa (maxillary, mandibular), buccal mucosa (right, left), lateral and ventral tongue (right, left), floor of the mouth and lingual frenum, soft palate and fauces	Compound score generated from sum of average ulceration score and average erythema score. Adaptation of OMAS (Sonis et al, 1999)
Bruya et al, 1975	13 items scored from 1 to 3: 5 items assess physical status (level of consciousness, breathing, nutritional habits, ability to chew and ability to self-care) 12 items assess oral cavity: lips (texture, colour, moisture) tongue (texture, colour, moisture), mucous membrane, gingival tissue, saliva, teeth, taste, voice	
Dibble et al, 1996 (MacDibbs)	4 items scored from 0 to 3: pain, dryness, eating, talking, taste, saliva production, swallow, number of ulcers, presence of vesicles, red areas or white patches, size of largest ulcer in mm.	Also included potassium hydroxide smear and herpes simplex culture. Compound score.
Donnelly et al, 1992	5 items scored from 0 to 3: lesions, erythema, oral oedema, pain, dysphagia.	Compound score
Dudjak et al, 1987	8 items scored from 1 to 4: lips, mucous membranes, palate and oropharynx, gingivae, saliva, swallow, diet, taste and ability to self-care.	Adaption of Beck (1979) Compound score
Eilers et al, 1988 (OAG)	8 items scored from 1 to 3: voice, swallow, lips, tongue, saliva, mucous membrane, gingivae and teeth.	Compound score
Harris et al, 2006	Pain assessed in 5 locations from 0 to 10. Ability to swallow, eat and talk graded “able”, “with difficulty” or unable. Visual assessment (colour, presence of ulcers, white or red areas and dryness).	Pain tool Stomach, gut and anus also included in tool.
Kolbinson et al, 1988	8 sites scored: lips, mucosa (labial, buccal), palate (hard, soft), tongue (dorsal, ventral and floor of the mouth), gingivae. Atrophy, erythema, vascularity, ulceration, bleeding, and salivary viscosity assessed for each site and graded from 0 to 3.	Compound score

Author	Components included	Additional information
Kushner et al, 2008	9 sites scored using 10mm VAS for erythema and ulceration: upper/lower lip, right/ left inner cheek, floor of mouth, right/ left ventral and lateral tongue, soft palate and fauces, and hard palate. VAS also used for total erythema and total ulceration.	Modified OMAS score. Compound score
Kushner et al, 2008 (PROMS)	10 Visual analogue scales (VAS). Patients asked to indicate level of mouth pain, difficulty speaking and level of speech restriction due to mouth sores, difficulty eating hard and soft foods, restriction in eating due to mouth sores, difficulty and restriction in drinking due to mouth sores, difficulty swallowing due to mouth sores and change in taste.	Patient generated instrument
Lievens et al, 1998	2 items scored: mucositis (size of spotting) and dysphagia. Mucositis graded 0-6, dysphagia 0-4.	
Maciejewski et al, 1996	7 items scored: mucositis type, ulceration, dysphagia all graded from 0 to 4. Mucositis area, oedema, bleeding and odynophagia graded from 0 to 3.	Compound score
McGuire et al, 1993	9 sites scored: Mucosa (labial, right buccal, left buccal), tongue, soft palate, floor of the mouth, hard palate, gingivae and lips. Severity of erythema scored from 0-3, extent of ulceration/ erythema scored from 0-4. Pain also assessed.	
McGuire et al, 2002 (OMI)	20 items scored 1-3: mucosa (labial, buccal), tongue (dorsal, lateral and ventral surfaces), floor of mouth and soft palate graded for atrophy, erythema, edema and size of ulceration and pseudomembrane (cm).	Compound score Authors provide a complex list of grading rules. Modified OMI score.
Öhrn et al, 2001	10 items assessed using VAS: pain, mouth dryness, ability to talk, salivary viscosity, dysphagia, ability to perform oral hygiene, alterations in taste, condition of the lips and gingivae and whether the patient feels that they have a clean mouth.	Patient reported measures.
Olson et al, 2004	3 items scored from 0 to 3: lesions, erythema and bleeding	Compound score Modified WCCNR grading scale. Instrument grades signs not areas.
Passos et al, 1966	8 items scored from 1 to 3: saliva, tongue, palates, membranes and gums, teeth, odour, lips and nares	Compound score
Potting et al, 2006	6 items scored from 0 to 3: erythema, oedema, lesions, pain, dryness, viscosity. Lips, uvula and tonsillar crypts, and oral mucosa of the gingival palate examined for the 6 items scored.	Instrument grades signs not areas.

Author	Components included	Additional information
Raether et al, 1989	Percentage of ulceration accessed for 7 sites: mucosa (buccal and labial, alveolar mucosa) gingival, hard palate, soft palate and oropharynx, floor of the mouth and ventral surface of tongue, and dorsal surface of the tongue.	Compound score
Schubert et al, 1992 (OMI)	34 items scored from 0 to 3: atrophy and pseudomembrane assessed at 11 sites each: lips (upper lower), labial mucosa (upper and lower), buccal mucosa (right and left) tongue (dorsal, lateral and ventral tongue), soft palate and floor of the mouth. Erythema not assessed in soft palate. Edema assessed for buccal mucosa (right and left)	Compound score
Sonis et al, 1999 (OMAS)	9 sites graded from 0 to 3 for ulceration/ pseudomembrane and 0 to 2 for erythema: lips (upper and lower), cheeks (right and left) ventral and lateral tongue (right and left), floor of the mouth, soft palate and fauces and hard palate.	Compound score
Spijkervet, 1989	8 sites graded: buccal mucosa (left and right), hard and soft palate, dorsum and border of the tongue (left and right), floor of the mouth. Each site graded from 0 to 4(no mucositis to ulceration), length of erythema/ ulceration also graded from 1 to 4.	Compound score. Complex calculations required.
Stiff et al, 2006 (OMDQ)	6 questions incorporating 8 items : diarrhoea, mouth and throat soreness, swallow, drinking, eating, talking, sleeping, overall health	Patient reported instrument
Tardieu et al, 1996 (DIM)	8 categories incorporating 16 items: lips, gingival, mucosa, tongue all scored from 0 to 3 for aspect, colour and dryness (12 items), swallow, saliva, talking and pain, scored 0-3 (4 items).	Compound score
Van Drimmelen and Rollins, 1969	7 categories incorporating 8 items scored from 1 to 3: palates (moisture, debris), tongue (coating, moisture), membranes (moisture, debris), gingivae, teeth, lips (moisture, general condition) odour	Compound score
Walsh et al, 1990	10 items: voice, swallow, lips, tongue, buccal mucosa, hard and soft, palate, gingival, saliva production and teeth all scored, from 0 to 2. Patient self assessment scored 0 to 3.	Compound score
Weisdorf et al, 1989	7 sites scored 0 to 3: tongue, gingivae, hard palate, mucosa (buccal, alveolar), floor of the mouth, soft palate. Percentage area of mucosal ulceration also recorded.	Compound score

DIM=Daily index of mucositis, OAG=Oral assessment guide, OMAS=Oral mucositis assessment scale, OMDQ=Oral mucositis daily questionnaire, OMI=Oral mucositis index, PROMS=Patient reported oral mucositis scale,

6.5 Discussion

This review identified 50 instruments previously used for the assessment of oral mucositis in adults. The attributes and problems with these instruments identified will now be discussed.

6.5.1 Simple scales

Simple scales are generally quick and easy to use making them perfect to use in busy outpatients' clinics. However, one of the tools shown in Table 11 was simplistic to the point of being facile. The Chapko and colleagues (1991), instrument graded mucositis on a scale from zero to four: "mild", "moderate", "severe' and "life threatening", with no additional descriptors. Exactly what constitutes "life-threatening" mucositis is not clear, and no information was provided about the actual component of mucositis being scored. The severity of pain and nausea were also assessed using the same five point scale, which may explain the terminology used. The use of such a tool in either clinical practice or a clinical trial would necessitate extensive training of personnel to define such differences, and even if this was achieved, it is likely that distinctions between moderate and severe would depend on assessor experience of severe mucositis.

Simple scales have been criticised because the criteria used in these instruments may be open to interpretation (Potting et al., 2006). Twelve of the instruments presented in Table 11 assessed the oral cavity using a zero to four scale. The researchers developing the Western Consortium for Cancer Nursing (WCCNR) instrument hypothesised that distinction between grades two and three is difficult in simple scales, and leads to poor inter-observer reliability (Anonymous, 1991). However, the authors then undermined their argument by putting forward a scale with only three grades, which, while possibly addressing the inter-observer reliability issue, had the potential to hide the true extent of the problem by classifying both moderate-to-severe and severe cases of mucositis as a grade 3, therefore removing the potential to define between them. Such a distinction may be clinically relevant.

The World Health Organisation (WHO) and Radiation Therapy Oncology Group (RTOG) instruments have frequently been used to assess mucositis in clinical trials

(Quinn et al., 2008, Sonis et al., 2004, Worthington et al., 2007). Both instruments assessed pain, erythema and ulceration using a scale of zero to four. However, the WHO also included the patient's ability to swallow solid food and ability to drink liquids (World Health Organization (WHO), 1979). Neither of these instruments have been validated. However, Quinn noted that the WHO instrument is based on expert opinion and has been used for nearly 30 years (Quinn et al., 2008).

6.5.2 Multi-component instruments

Multi-component scales provide an abundance of information about changes occurring in the oral cavity. They are therefore an excellent resource for use in clinical trials. However, while these instruments provide useful information about the condition of the oral cavity, many of these instruments requires extensive and sustained examination of the oral cavity, and it is likely that the patient will have to keep their mouth open for an extensive period of time during assessment, or alternatively, repeatedly open and close their mouth, which could be distressing for a patient who was in a great deal of pain, and completely impractical in a patient suffering from any of the symptoms clustered with OM, such as nausea or vomiting (McGuire et al., 1998).

In twenty-one of the multi-component instruments shown in Table 12, a total score was generated by combining the sub-scores in each category. This score can be achieved through a number of means and this therefore may result in the clinical meaning of the score becoming altered or in an important change being missed because it is masked by other changes (Olson et al., 2004). An improvement in the appearance of the mucous membrane in a patient screened repeatedly using the Oral Assessment Guide (OAG), for example, may be masked by an increase in the level of plaque on the patient's teeth, leading to the decrease in mucous membrane score being hidden by an increase in the score of the teeth category, and therefore no overall change in score. The OAG has additionally been criticised because this instrument graded categories that are not specific to mucositis. Therefore a patient with another condition, for example hepatic lesions, had the potential to score highly on this tool without actually suffering from oral mucositis (Dibble, 1996).

Three multi-component assessments instruments identified in Table 12 require more complex mathematics than simple addition or subtraction to assign a grade, which precludes the use of these instruments in everyday clinical practice, and may increase both researcher burden and increase the risk of miscalculations in research. It is also difficult to imagine these instrument being routinely used in clinical trials, due to the amount of training that research staff would require before accurate data collection could be ensured. In addition, the use of Spijkervet and colleagues scale is made difficult by the amount of continual observation required to accurately measure the oral cavity, and the use of a 2cm gauge to assess the size of ulceration. This is likely to be uncomfortable and fatiguing for the patient, especially if a researcher had never previously used this instrument.

In addition to the Spijkervet instrument, a number of other scales employed the use of measurement devices to assess the oral cavity. Five simple scales grade ulceration based on size (Carl and Emrich, 1991, Damon et al., 2004, Ferretti et al., 1988, Trotti et al., 2000, Van der Schueren et al., 1983). A ruler or gauge would have to be used with these instruments. The MacDibbs instrument, a multi-variable scale, employed the use of a periodontal probe to measure depth of ulceration (Dibble, 1996). The authors did not give any information about whether the use of the instrument caused pain or discomfort to the patient, in fact, no literature at all was identified that detailed the suitability of the assessment process to the patient. The recent European group for Bone Marrow Transplant (EBMT) guidelines on the assessment of OM in adults stated that excessive touching of the injured mucosa could result in worsening of the damage, and therefore such examinations should be short and precise (Quinn et al., 2008). It is possible that the use of such a periodontal probe, especially by a researcher new to its use, could result in greater irritation of the oral cavity and patient distress. For this reason, the EMBT guidelines recommended that the Oral Mucositis Index (OMI) and MacDibbs instruments (Dibble, 1996, McGuire et al., 2002, Schubert et al., 1992) should only be used after all other alternatives have been considered and discounted (Quinn et al., 2008).

6.5.3 Objective versus subjective and functional items

In addition to separating instruments into simple and multi-component scales (Parulekar et al., 1998), they can also be separated into instruments containing objective items, those containing subjective or functional items, or a combination of two or more (Tomlinson, 2008). The inclusion of subjective items in oral assessment instruments is a contentious issue. Sonis and others (2004), argued that mucositis damage should be scored objectively and separately from assessment of functional (ability to eat or drink) and subjective (pain) variables, as functional items, such as the ability to eat, may not be related to mucositis. The authors pointed out that a number of instruments included the use of parenteral nutrition as an indicator of severe mucositis (National Institute of Health, 1993, Turhal et al., 2000). Some hospitals have policies of automatically placing transplant patients on parenteral nutrition, or alternatively prescribing such support due to intestinal toxicity, when the patient is still able to eat and drink. In such instances, the use of these instruments would result in overestimation of mucositis severity (Sonis et al., 2004). However, two of the instruments shown in Table 11 use the requirement for parenteral nutrition in addition to other criteria such as 'severe ulceration'(Byfield et al., 1985, Pitten et al., 2003). The use of such instruments would probably not result in over-estimation of severity as other criteria for assessment exist. The choice of instrument for mucositis assessment should take into account hospital policy, therefore reducing the possibility that other factors could result in overestimation of mucositis severity. In addition, training of staff to recognise if the use of nutritional support, or the patient's reluctance to eat or drink, was due to mucositis, or some other factor, and grade accordingly would also help in this area.

The authors of the EMBT guidelines (Quinn et al., 2008) disagreed with the opinion of Sonis and Colleagues (2004), stating that assessment should be conducted using an instrument that can measure the physical, functional and subjective changes of the oral cavity, and that if such a tool is not available, a combination of instruments should be employed (Quinn, 2008). The authors did however note that assessment of functional symptoms should be conducted prior to any assessment of the oral cavity (Quinn et al., 2008). Tardieu and colleagues (1996), presented an instrument that allowed the examiner to assess the oral cavity using a combination of subjective and objective or purely objective criteria (Tardieu et al., 1996). The Tardieu and colleagues daily index of mucositis (DIM) instrument included 12 objective items and four subjective

categories: pain, swallow, dryness of the oral cavity and talking. This instrument was designed so that subjective categories could be removed if warranted (Tardieu et al., 1996).

6.5.4 Pain

The inclusion of pain assessment in 29 of the instruments shown in Table 11 and Table 12 is notable, as pain measurement in oral assessment instruments is controversial (Tomlinson et al., 2008). Jaroneski (2006), argued that as pain is a distressing component of mucositis reported by patients, the use of a pain scale is essential in assessment (Jaroneski, 2006). Conversely, it has also been argued that the use of analgesia may result in the underscoring of this pain (Sonis et al., 2001, Tomlinson et al., 2008). Pain assessments included in the instruments identified in this review can be separated into two groups: those which grade pain as mild, to severe, and those which assign a grade to pain based on the requirement for different grades of analgesics. The DIM instrument developed by Tardieu and colleagues (1996), does the latter, grading pain assessment on a scale from zero to four, and incorporating the requirements for minor analgesics (such as paracetemol) and major analgesics (morphine) (Tardieu et al., 1996). The under-reporting of pain due to the use of analgesia would not be a concern with the use of this instrument, as it employed the use of analgesia as a proxy for pain when assessing this category.

The EBMT guidelines stated that patient reports of pain should be included in oral assessments, and recommended the use of a visual analogue scale (VAS) to record such information (Quinn et al., 2008). Two recently developed instruments reported entirely patient reported symptoms, including pain, using VAS. Both these instruments were developed for patients undergoing bone marrow transplantation (Kushner et al., 2008, Stiff et al., 2006). Stiff and colleagues (2006), produced the oral mucositis daily questionnaire (OMDQ) for patients undergoing autologous transplantation (Stiff et al., 2006). This instrument was comprised of six questions, and asked patients to score their overall health, the amount of mouth and throat soreness that they have experienced in the previous 24 hours, how much this soreness had affected their ability to perform activities (swallowing, talking, eating, drinking, talking), how they would rate this soreness, how much diarrhoea they had experienced during the same timeframe, and

how they would rate this diarrhoea (Stiff et al., 2006). The Kushner instrument was developed for use in allogeneic transplantation. This instrument is slightly longer than the Stiff and colleagues instrument, and asked the patients to complete 12 VAS about their level of mouth pain, whether they had any difficulty speaking due to ulceration, difficulty eating hard and soft food, their level of restriction in eating, their difficulty drinking due to ulceration, any level of restriction in drinking, if they had difficulty swallowing and any change in taste (Kushner et al., 2008). Both these instruments have been validated by the authors at the point of development.

6.5.5 Modifications of previous instruments

Ten of the instruments shown in Table 11 and Table 12 are modifications or updates of previous instruments. The recently updated National Cancer Institute instrument (NCI CTC version 4) assessed mucositis using patient reports of pain and the patient's ability to eat and drink to assign a grade. Pain was defined as moderate if it did not interfere with oral intake, and severe if it did (Cancer Therapy Evaluation Program, 2009). Previous versions of this scale also included the assessment of ulceration and erythema and it is not clear why the authors felt that the omission of these items was necessary. The removal of such items has resulted in an instrument that could be used to grade mucositis without requiring the patient to open their mouth. In addition, it could be argued that the removal of any mention of erythema or ulceration has resulted in an instrument that could be used to measure a number of different oral conditions, and not specifically mucositis.

It is possible that the psychometric properties of an assessment instrument may be altered by the modification of its components (Eilers and Epstein, 2004). Many of the instruments shown in Table 11 and Table 12 have been modified without the authors providing a rationale for such changes and, with the exception of the revised WCCNR and 20-item OMI instruments (McGuire et al., 2002, Olson et al., 2004), without testing of the validity or reliability of the modified instrument. McGuire and colleagues modified the OMI that was previously developed by Schubert and colleagues (1992), changing the number of items assessed using this instrument from 34 to 20 items, before validating the new instrument. These modifications were made to make the instrument easier to use for non-dental health professionals (McGuire et al., 2002). However, this

instrument is still very complex. In addition to a set of instructions for using the instrument, the authors also provided a list of grading rules that incorporated a decision tree, which even in small text took up more than half a page of the journal article.

6.5.6 Reliability and validity information

The CCLG review of oral assessment instruments found that, of the 54 instruments identified in the search, only 15 of them had any form of validity or inter/ intra-rater reliability testing (Gibson, 2010). Of these 15 instruments, three were for use in children and therefore not suitable for use in a clinical trial with adults (Chen et al., 2004, Gibson et al., 2006, Sung et al., 2006). Table 13 shows the validity and reliability assessments for the 12 instruments designed for use in adults. These instruments were assessed using an adaptation of the diagnostic check-list (Scottish Intercollegiate Guidelines Network (SIGN), 2002). Eight instruments reported inter-rater reliability information: the amount of agreement between the scores generated by two researchers assessing the oral cavity independently; while only three instruments reported intra-rater reliability: the amount of agreement between repeated oral assessments performed by the same researcher (McGuire et al., 2002, Stiff et al., 2006, Tardieu et al., 1996). Five studies reported face validity, which was defined as whether the instrument accurately measured what it was designed to assess (Gibson et al., 2010). However, all instruments were felt by the authors to measure the condition of the oral cavity. Six instruments reported content validity, a measure of the comprehensiveness of the instrument, while criterion validity, the comparison of the instrument with another oral assessment instrument, was reported for six instruments. However, adequate blinding of researchers to the results of the other assessment scale was only employed by one study (Kushner et al., 2008). Lastly, construct validity, defined as the testing whether the instrument assesses what it was designed to, was reported by three studies (Kushner et al., 2008, McGuire et al., 2002, Spijkervet et al., 1989a). Only one study, the 20-item OMI (McGuire et al., 2002) reported content, face criterion and construct validity. However, it should be noted that the use of this instrument was specifically warned against, unless all alternatives had been discounted, by the EMBT guidelines, due the level of extensive oral examination required (Quinn et al., 2008)

Table 13: Assessment of studies, using adapted 'Diagnostic studies' checklist, reporting validity/reliability testing of oral assessment tools

	Dibble 1996	Donnelly 1992	Eilers 1988	Kushner 2008	McGuire 2002	Olson 2004	Potting 2005	Sonis 1999	Spijkervet 1988	Stiff 2006	Tardieu 1996	WCCNR 1991
PARTICIPANTS												
Was selection bias avoided?	N	Y	Y	N	U	U	Y	Y	U	Y	Y	U
Did the study include an appropriate spectrum of participants?	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
RELIABILITY												
Inter-rater measured?	Y	N	Y	N	Y	Y	Y	Y	Y	N	Y	N
Was the duration between assessments suitable so as not to have allowed a true change in oral health status?	U	-	Y	-	Y	Y	Y	Y	Y	-	Y	U
Intra-rater measured?	N	N	N	N	Y	N	N	N	N	Y	Y	N
Was the duration between assessments suitable so as not to have allowed a true change in oral health status?	-	-	-	-	U	-	-	-	-	Y	U	-
VALIDITY												
Was face validity reported?	N	N	N	Y	Y	N	Y	Y	Y	N	N	N
Do you feel the tool appears to measure the condition of the	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

	Dibble 1996	Donnelly 1992	Eilers 1988	Kushner 2008	McGuire 2002	Olson 2004	Potting 2005	Sonis 1999	Spijkervet 1988	Stiff 2006	Tardieu 1996	WCCNR 1991
mouth?												
Was content validity reported?	Y	N	Y	N	Y	N	Y	Y	N	N	N	Y
Were appropriate experts consulted in the development of the tool and/or a rigorous evaluation of the literature?	Y	-	Y	-	Y	-	Y	Y	-	-	-	Y
Does the tool address all the -attributes of the -concept under investigation?	Y	-	Y	-	Y	-	Y	Y	-	-	-	Y
Does the tool include any irrelevant items?	N	-	N	-	N	-	N	N	-	-	-	N
Was criterion validity reported?	N	N	N	Y	Y	Y*	N	N	Y	Y	N	Y
Was the test compared with a valid reference standard?	-	-	-	Y	Y	Y*	-	-	Y	Y	-	Y
Were the test and reference standards measured independently (blind) of each other?	-	-	-	Y	U	U	-	-	U	N	-	U
Was the choice of patients for assessment by the reference standard independent of the test's results?	-	-	-	Y	U	U	-	-	Y	-	-	U
Was the reference standard measured before any	-	-	-	U	U	U	-	-	U	-	-	Y

	Dibble 1996	Donnelly 1992	Eilers 1988	Kushner 2008	McGuire 2002	Olson 2004	Potting 2005	Sonis 1999	Spijkervet 1988	Stiff 2006	Tardieu 1996	WCCNR 1991
interventions were started with knowledge of test results?												
Was construct validity reported?	N	N	N	Y	Y	N	N	N	Y	N	N	N
Do you feel there is good justification for the theoretical construct used?	-	-	-	Y	Y	-	-	U	Y	-	-	-

N=No, Y=Yes, U=Unclear, *radiotherapy only, Adapted from Gibson, 2010 (permission granted)

It is of concern that of the 50 assessment instruments identified in this review; only 10 of these have been reported as validated. A number of the non-validated instruments shown in Table 11 and Table 12 are routinely used in both clinical research and practice, which is worrying considering that even basic testing, such as inter-rater reliability testing, has not been conducted using these instruments. It is also of concern that there does not appear to be a trend towards newer instruments being more likely to be validated than older instruments, as 7 of the validated instruments shown in Table 13 are in excess of 10 years old. Although, it should be noted that both of the recently developed patient generated instruments (Kushner et al., 2008, Stiff et al., 2006) have both been validated.

6.5.7 Choice of instruments for a RCT conducted in patients undergoing stem cell transplantation

6.5.7.1 Simple scales

It is acknowledged that the WHO instrument has not been validated, and therefore it could be argued that the choice of this instrument for use in the feasibility study is questionable. However, it was chosen because it was the most frequently employed instrument in the studies assessed for ROB, being used in 32 of the 133 included studies (24%). The use of this instrument in the feasibility study would permit comparison with the results of other studies and would allow the results of the feasibility study to be a potential inclusion in the Cochrane prevention review (Worthington et al., 2010). This is therefore a suitable choice of simple scale for use in the feasibility study.

6.5.7.2 Multi-component instruments

Seven of the multi-component instruments shown in Table 13 have been validated in patients undergoing BMT (Donnelly, 1992, Eilers et al., 1988, Kushner et al., 2008, McGuire et al., 2002, Potting et al., 2006, Stiff et al., 2006, Tardieu et al., 1996). It is therefore most appropriate to choose one of these seven instruments to use in the feasibility study. However, two of these instruments were identified after the ethics application for the trial was submitted (Kushner et al., 2008, Potting et al., 2006), leaving five instrument to choose from. The use of the 20-item OMI (McGuire et al., 2002) is not recommended by the EMBT guidelines, and therefore is not an appropriate instrument for the feasibility study (Quinn et al., 2008). The OAG included a category that is not specifically related to mucositis (teeth) (Eilers et al., 1988), and since this

instrument could be argued to be an assessment instrument which grades the condition of the oral cavity, rather than mucositis, it is not an appropriate choice for the feasibility study. One the three remaining instruments, Donnelly (1992), has not been investigated for inter and intra-rater reliability, and is therefore not an appropriate choice for use in a clinical trial. The DIM (Tardieu et al., 1996) is an instrument which assesses both the objective and subjective components of mucositis and provides a large amount of information about the status of the oral cavity because it assigns a grade by site (mucosa, gingivae, lips, tongue), rather than just the overall. It is therefore a good choice for use in association with the WHO instrument, which provides more basic information. As patient reports of mucositis have been identified as under-reported in the literature elsewhere in this thesis, it seems appropriate to also employ the use of a patient generated screening instrument in the feasibility study. The OMDQ is a patient generated instrument which asks patients to grade level of mouth and throat soreness and the impact their oral symptoms have on their ability to eat, swallow, talk, drink and sleep (Stiff et al., 2006).

6.5.8 Limitations of this review

This review has a number of limitations. All oral assessment instruments identified in this review were in English. This was despite the systematic search being conducted without language restriction. It is extremely likely that a number of non-English oral assessment instruments exist, and this review should therefore be considered to only provide an overview of oral assessment instruments written in English. Another limitation of this review is that, with the exception of reliability and validity information, no attempt was made to assess the quality of the oral assessment instruments, due to a lack of consensus regarding how best to do this in these instruments.

6.6 Conclusion

This review has identified 50 multi-component instruments in the literature. However, only 12 of these instruments have been validated. Three instruments have been selected for use in a clinical trial: the Tardieu instrument (DIM) and the OMDQ instrument (Stiff et al., 2006, Tardieu et al., 1996). Both of these were developed for use in the transplant population. One non-validated simple scale was also identified for use: the WHO

instrument (World Health Organization (WHO), 1979). Copies of these three instruments can be found in Appendix 3. Further details of the use of these instruments are included in the protocol chapter, which is presented next. In addition, this protocol chapter will describe the use of one further assessment instrument: a nutritional assessment tool.

Chapter 7: Protocol Development and Feasibility Trial Methods

This chapter details the process of protocol development and builds upon the results of previous chapters (Figure 2). The methods of the feasibility study are presented along with the rationale for any decisions that have been made.

7.1. Study design, setting, aim, objectives and outcome measures

7.1.1 Study design

A prospective randomised double blind placebo control trial design was employed.

7.1.1.1 Choice of a phase III design

There are four different phases of clinical trials. Phase I trials are the first earliest phase of trial development (Braveman, 2010). In this phase, a new intervention is tested in order to identify the maximum tolerated dose which can be given of the drug before patients experience unacceptable adverse events (Friedman et al., 1998). A dose escalation design is commonly used in these trials, whereby a small dose is given to cohort of patients to determine toxicity, and if this is not identified then a larger dose is then administered. This continues until an unacceptable level of toxicity is reached and the study terminated. In phase II studies, the biologic effects and adverse events of the intervention are determined. Various designs for phase II trials have been put forward: Simon and colleagues (1985) suggested a design whereby patients are randomised between two or more treatment arms. The trial is then conducted and the response rate for each arm assessed and the treatment arm with the highest response rate are chosen for further study. This method of comparison has also been adapted to incorporate the use of historical control groups , which allow for arms of the study to be terminated in the event of adverse events (Rubinstein et al., 2005). Other designs which incorporate a randomised standard treatment arm or phase II/III design have also been suggested (Rubinstein et al., 2005).

Phase III trials include a control arm and are conducted to determine the effectiveness of a particular intervention. These trials are conducted prospectively, and aim to obtain a definitive answer about whether the intervention is effective; close monitoring of side

effects are also a key theme of these studies (Braveman, 2010). Phase IV trials are commonly conducted after a drug has been marketed, and aim to study adverse events over a longer duration. These studies last several years and are often used to study the effects of an intervention in groups of patients not included in earlier studies (Braveman, 2010).

It was decided to use a phase III design for this feasibility study for a number of reasons: As vitamin E was already used as a supplement, and trials have already identified the maximum tolerated dose and adverse events for this product, it was felt that the use of a phase I trial design was redundant. A phase II design was therefore thoroughly considered, but was eventually rejected, as neither a therapeutic dose nor a dose response relationship for vitamin E has been identified in the, quite extensive, literature on the prevention or treatment of chemotherapy side effects, including mucositis. The researcher was therefore concerned that a phase II study could be conducted which could fail to identify a therapeutic dose. A phase III design which employed a placebo control arm was therefore selected, in order to determine the effectiveness of the intervention. However, before such a study could be conducted it was decided to first conduct a feasibility study to explore the issues surrounding this design.

7.1.2 Setting

This was a single site study conducted on the haematology unit of a cancer hospital in the North West of England. The unit could accommodate 20 patients in private side rooms.

7.1.3 Aim

To assess the feasibility of conducting a trial to explore the effectiveness of d-α-tocopherol in the prevention of oral mucositis compared to a soya bean oil placebo, over and above standard care, in a sample of patients undergoing conditioning for bone marrow transplantation.

7.1.4 Main objectives

- To explore the recruitment, retention and adherence of patients in an RCT of patients undergoing bone marrow transplantation.
- To explore the suitability of pharmacy release, methods of blinding and adverse event reporting in this setting
- To explore the suitability of the tools used for outcome assessment (WHO, DIM, PG-SGA, OM-DQ).

7.1.5 Secondary exploratory objectives

- To compare the duration of ulcerative mucositis measured using the WHO instrument in the intervention group to those of the control group
- To compare the highest mucositis grades measured using the WHO instrument
- To compare the highest mean mucositis scores generated by the Daily Index of Mucositis (DIM) instrument
- To compare the pattern of mucositis measured using the WHO instrument over time between the two groups
- To compare the pattern of mucositis measured using the DIM instrument over time between the two groups
- To compare patients' reports of oral pain between the groups
- To compare mean nutritional screening scores between the groups

7.1.6 Study outcome measures

As this was a feasibility study, data collected in this study was used to assess the practicality of patient recruitment and the expected rate of recruitment for a larger study, the suitability of the randomisation, blinding and allocation concealment procedures, and the number of adverse events and protocol violations. The suitability of the data collection instruments was also considered. It was planned that data collected during this study would be used to inform sample size calculations for a larger study.

7.2. Sample size

It was planned that 60 patients (30 per group) would be recruited to take part in the feasibility study. This figure was chosen after considering that approximately 84 patients underwent treatment in the Haematology unit in 2007 and that the unit was

substantially expanded to accommodate more patients early in 2008, and that in order to estimate a parameter, such as a mean or median value, 30 patients or greater are required (Lancaster et al., 2004). The rate of drop out for this study was estimated at 30%. In addition, it was planned to recruit six patients to take part in the pilot. The pilot was planned to ensure that patients were able to follow the protocol and to check that the data collection sheets were adequate.

7.3 Recruitment, informed consent, randomisation, allocation concealment and blinding

7.3.1 Recruitment

All patients fitting the inclusion criteria were identified using the hospital database and from discussions with Clinicians. All eligible patients were approached by a member of the medical team to ask them if they would be interested in speaking to the researcher. The researcher spoke to the patient about the study and gave them a patient information sheet to read. Patients were also informed that participation in the study was voluntary and that any decision not to enrol would not affect their treatment options. Patients choosing to enrol in the study were informed that they could remove themselves from the study at any time, and that this decision would not affect their standard of care.

7.3.2 Recruitment of non-English speaking patients

The recruitment of non-English speaking patients to research is an on-going difficulty in clinical trials (Jiwa, 1999). While it is evident that patients who fall this group should not be discriminated against by a policy of non-recruitment, the fact remains that recruitment in this area is difficult and produces additional consent issues. For the feasibility trial, it was planned to use the hospital translation team to help speak to patients who did not speak English as a first language.

7.3.3 Informed consent

The researcher returned to speak to the patient a minimum of 24 hours after the first approach, to ask the patients if they were willing to take part in the study and to answer any questions patients may have had. Those patients willing to take part in the study were then asked to sign the consent form. Three copies of the content form were signed:

the master copy was placed in the study file, one copy was retained by the patient, and the remaining copy was filed in the patient's notes.

7.3.4 Randomisation

The randomisation was computer generated by an independent statistician from the department of Nursing, Midwifery and Social Work at the University Of Manchester. The pharmacy department at the hospital held a copy of the randomisation sequence. Additional copies of this sequence were held by the researcher's supervisors until the end of the study. At baseline (the day before starting chemotherapy), prior to randomisation, basic demographical data were collected: age, gender, smoking status, diagnosis, treatment (type of transplant), and current (if any) use of supplements.

7.3.5 Pharmacy release

Once the patient had been recruited to the study they were assigned the next number in sequence, the pharmacy release form was signed by a doctor and the pharmacy was contacted and asked to dispatch the drug container with the same number. Checks by the hospital pharmacy prevented the containers being dispatched out of order.

7.3.6 Blinding and allocation concealment

This study was a double blind RCT. Both the patients and the outcome assessor were blind to the treatment allocation. The allocation sequence was concealed using pre-packed bottles which were identical in appearance and sequentially numbered. In addition, the use of the hospital pharmacy to dispense the intervention and placebo products also ensured adequate allocation concealment.

7.4 Inclusion and exclusion and withdrawal criteria

This study recruited adults diagnosed with haematological malignancies (Lymphoma, Leukaemia and Multiple Myeloma) undergoing conditioning for both allogeneic and autologous transplantation. This population was chosen because they are at risk of developing severe mucositis due to the high doses of chemotherapy used for conditioning. The exclusion criteria consisted of patients undergoing conditioning for

other cancers, children, and patients who were allergic to soya or who took exception to gelatine, which was an ingredient in the capsules. Patients with oral mucositis at baseline, or those prescribed warfarin, were also excluded. As the ethics committee were concerned that oral mucositis may be confused with other types of ulceration, patients prescribed bactrim or clarithromycin antibiotics at baseline, were also added to exclusion criteria, as these drugs may be associated with oral ulceration.

The inclusion and criteria were not checked against admissions onto the unit prior to starting the study, as the researcher would have required ethical and trust approval to access patient notes. However, the inclusion and exclusion criteria were discussed with two of the Consultants on the unit before the application for ethical approval was made, and the overall opinion was that the vast majority of patients admitted to the unit would meet the inclusion criteria. It should be noted that only one potential participant screened prior to recruitment did not meet the inclusion criteria for the study, due to their use of warfarin.

The expansion of the unit increased the number of transplant spaces available and therefore subsequently the number of patients who were referred to the hospital from other hospitals both from within the UK, and from abroad. It was expected that approximately 120 patients would be treated on the unit between June 2008 and July 2009, and after careful study of the transplant planning lists, this figure appears to have been correct. It was calculated by the statistician that 66 patients would be needed to be recruited for the study. This was based on the literature which suggested that 30 patients were required to estimate a parameter such as a mean (Lancaster et al., 2004). This was interpreted conservatively by the statistician, who decided that 30 patients would be required in order to calculate a mean, and another 30 would be required to estimate a standard deviation, and that another six would be required for the small pilot at the beginning of the study. It is arguable that the likelihood of recruiting 66 patients during the trial was over-estimated during the process of setting up the study on the unit. Conversely, it could also be argued had the problems with clinical staff not been experienced, the level of recruitment into the trial would have been great enough to at least allow for an adequately powered calculation of parameters.

A number of different steps were taken in an attempt to increase the recruitment of patients into the study after the issues with clinical staff were experienced. The easiest way to increase the numbers in the pool of available patients would have been to increase the number of study sites, and therefore change the study design from a single to a multi-site study. To determine if this was a possibility, consultants at another hospital were approached informally to gauge their reaction. Unfortunately, they were unable to help due to other trials being conducted on the unit and therefore the study remained a single site study. The inclusion and exclusion criteria were also reassessed but it was found not to be possible to widen the already relatively broad criteria.

7.4.1 Inclusion criteria

Both male and female subjects were recruited to take part in the feasibility study. The inclusion criteria were as follows:

- Patients aged 18 years old or over.
- Patients diagnosed with Multiple Myeloma, leukaemia or lymphoma
- Patients planned to undergo conditioning for BMT transplantation
- WHO mucositis score of 0
- Patients not enrolled in other oral mucositis trials
- Patients treated as inpatient

7.4.2 Exclusion criteria

The exclusion criterion consisted of the opposite of the inclusion criteria listed above and in addition included:

- Patients who had a religious or dietary exception to gelatine.
- Patients who were being prescribed warfarin.
- Patients who had an allergy to soya lecithin.
- Patients prescribed septrin (bactrim) at recruitment
- Patients prescribed clarithromycin at recruitment
- Patients prescribed any drug other than chemotherapy/radiotherapy that in the opinion of a Clinician might have caused mucositis.

7.4.3 Withdrawal criteria

The withdrawal criteria for this study were as follows:

- Patient withdrew their consent to take part in the study.
- Patient suffered a suspected unexpected adverse event (SUSAR).
- Patient lost capacity

If a patient asked to withdraw during the study, they were given the option of stopping the supplementation but continuing with oral screening, pain and nutritional assessments.

7.5 Treatment Arms

7.5.1 Intervention group

The intervention group was provided with capsules of natural source D-α-tocopherol in a dosage of 1000iu (670mg). This capsule was purchased from Healthplus (Dolphin House, 27 Cradle Hill Industrial Estate, Seaford. East Sussex, BN25 3JE) and was produced in France by Capsugel (Ploërmel, ZI de Camagnon, BP 320, 56803 Ploermel, Cedex, France).

7.5.2 Control group

The control group were provided with a placebo containing soya bean oil in a gelatine capsule. This capsule was purchased from Healthplus (Dolphin House, 27 Cradle Hill Industrial Estate, Seaford. East Sussex, BN25 3JE) and was produced in France by Capsugel (Ploërmel, ZI de Camagnon, BP 320, 56803 Ploermel, Cedex, France).

7.5.3 Finding a supplier

An extensive search was conducted for a company who could supply both vitamin E and a suitable placebo product. Healthplus was eventually chosen due to their close working relationship with Capsugel (the manufacturer of the intervention and placebo). Healthplus approached Capsugel on behalf of the Researcher to ask if it was possible for them to manufacture placebo capsules of the same size and shape as the intervention for use in this study. Capsugel suggested soya bean oil as a placebo as it was a relatively

cheap ingredient already included in the vitamin E capsules. As neither Capsugel or Healthplus held a manufacturer's authorisation for investigation medicinal products (MA-IMP) license, an authorisation required by the MHRA for products used in clinical trials, the researcher arranged for the intervention and placebo capsules to be repackaged by Preston Pharmaceuticals under their MA-IMP licence, in sequentially numbered containers of identical appearance, which had the additional benefit of ensuring adequate allocation concealment.

There has been little consistency in previous studies investigating vitamin E in patients receiving chemotherapy, and a variety of doses of between 600mg (600IU[32]) and 2147mg (3200IU[33]) daily have been used (Argyriou et al., 2006a, Argyriou et al., 2006b, Blanke et al., 2001, Legha et al., 1982, Martin-Jimenez et al., 1986, Perez et al., 1986, Sung et al., 2007, Weitzman et al., 1980, Wood, 1985). The dosages used in these previous studies have been well-tolerated and no negative effects on chemotherapy efficacy have been identified. As Healthplus, sold vitamin E in either doses of 500iu (335mg) or 1000iu, a single dose of 1000iu (670mg) of D-alpha-tocopherol, was chosen for this study. The placebo capsules were manufactured in exactly the same way as the intervention using the same raw materials; however, soya bean oil was added instead of vitamin E.

7.5.4 Justification for the dose

The dose used in this study (670mg/1000iu) was chosen after consideration of the following factors: 1) that the literature on studies of similar interventions for the prevention of mucositis or other chemotherapy related side-effects had not conclusively demonstrated the appropriateness of any specific dose, and, 2) that significantly larger doses of vitamin E had been given to patients undergoing chemotherapy (see preceding paragraph) with no adverse effects reported. Healthplus was selected as the manufacturer of the intervention and placebo products; they were able to provide two different sized doses (500iu and 1000iu). Based on the factors listed above the larger dose of vitamin E was selected, careful consideration of the literature having identified no adverse effect of such a dose on chemotherapy efficacy. The adverse events

[32] As dl-alpha-tocopherol acetate (for more information see table 2)
[33] As d-alpha-tocopherol (for more information see table 2)

associated with such a dose are inconsistent in the literature and primarily have been reported in case reports or letters to the editor and not in RCTs. The use of the higher dose was hypothesised to be more likely to have an effect, and therefore the higher dose was selected based on the literature not having identified any consistent adverse events associated with such doses in RCTs.

7.5.5 Contraindications and toxicities

The toxicity of vitamin E is very low (Bendich and Machlin, 1988, Diplock, 1995, Kappus and Diplock, 1992), and doses of up to 3200 IU have not been associated with consistent adverse events (Kappus and Diplock, 1992). The majority of reports of adverse events in the literature have come from letters to the editor, case reports or uncontrolled trials, and have not been supported by the results of RCTs (Kitagawa and Mino, 1989, Meydani et al., 1998, Tsai et al., 1978). Such adverse events include gastrointestinal cramps and diarrhoea (Anderson and Reid, 1974, Gillilan et al., 1977), and fatigue and muscle weakness (Cohen, 1973). In addition, patients given large doses of vitamin E (1200iu/day) have shown prolonged clotting times due to hypoprothrombinemia in vitamin K deficient individuals (Bendich and Machlin, 1988). However, this may only be a concern for patients on anti-coagulant therapy, such as warfarin, a known vitamin K antagonist (Bendich and Machlin, 1988). Therefore patients prescribed warfarin were included in the exclusion criteria and were not recruited to take part in the study.

7.5.6 Vitamin E and chemotherapy

Block and colleagues (2007), systematically reviewed the impact of antioxidant supplementation on chemotherapeutic efficacy. The authors concluded that none of the trials included in the study reported a significant decrease in chemotherapeutic efficacy due to antioxidant supplementation and that many of the studies included in the review suggested increased survival times and tumour responses and fewer toxicities in patients treated with antioxidants than the controls (Block et al., 2007). Another review by the same authors incorporating a larger number of studies was published in 2008, and concluded that the use of antioxidants during chemotherapy has the potential to reduce dose-limiting toxicities (Block et al., 2008). Differences in treatment protocols and tumour types prevented the pooling of data in a meta-analysis in both these studies.

These results are also supported by a review by Drisko and colleagues (2003), who suggested that instead of exhibiting a negative effect, antioxidant supplementation may actually be of some benefit when combined with some chemotherapy regimens (Drisko et al., 2003). Further research into this area is ongoing.

It should be noted that while four studies which investigated the concurrent administration of vitamin E were included in the reviews conducted by Block and colleagues, all employed doses below that used in the feasibility study. However, studies which have administered vitamin E in higher doses than used in the feasibility study were included in a review by Conklin (2000), who identified no significant decrease in chemotherapy efficacy as a consequence of vitamin E administration. However, the author did note the potential for the use of an antioxidant tripeptide of cysteine, glycine and glutamic acid to interfere with the action of chemotherapy (Conklin, 2000), which suggested that the actions of different types of antioxidants on chemotherapy should be considered independently, and not as a class. As there are many different types of antioxidants, all of which work in a number of different ways, it would not be appropriate to discuss the impact of antioxidant supplementation on chemotherapeutic efficacy in term of a class effect, as not all antioxidants have the same effects, tolerability or safety profile (Evans et al., 2005).

7.5.7 Duration of vitamin E or placebo

In order to determine how many vitamin E capsules to order, the number of days a patient was expected to suffer from mucositis had first to be calculated. As a mean time for mucositis development has been suggested of between four (Wingard et al., 1991) and six days (Zerbe et al., 1992), with a median time for resolution of ulcerative symptoms of between nine (Spielberger et al., 2004) and 11 (Woo et al., 1993) days. It was therefore envisioned that patients would receive either vitamin E or placebo for approximately 15 days. However, as these figures are derived from historical values, which may be at risk of measurement bias, this figure was doubled to allow for unforeseen circumstances. Therefore a 30 day supply was ordered for each patient.

7.5.8 Instructions to patients

Patients were asked to take one capsule daily, place the soft gel capsule in their mouth, break it with their teeth, mix the resulting liquid with their saliva and swish this liquid around their mouths for 5 minutes before expectorating it. To maximise the time for the intervention to exhibit an effect, patients were asked take their capsule in the evening, and undergo the oral assessment the next morning. Patients were additionally asked to refrain from eating or drinking anything for at least 30 minutes after taking the capsule. Patients were asked to start taking the capsules daily on the evening before they received chemotherapy and continue taking the capsules until they met the exit criteria for the study (three continuous days with a WHO score of less than 2). Patients who were admitted to hospital on the day they started chemotherapy were asked to start taking the capsules in the evening of the same day.

7.6 Data collection procedures

7.6.1 Oral assessment

Patients had their mucositis scored using the WHO mucositis scale, and the daily index of mucositis (DIM) instruments. Copies of these scales can be found in Appendix 3. Baseline oral assessments were conducted on the day of admission prior to randomisation, and then daily until resolution of ulcerative mucositis. Ulcerative mucositis was considered to be resolved after the condition ceased to be ulcerative, shown by three continuous days of a WHO score of grade one or below. Mucositis scoring was conducted using a halogen light source to assess the patient's oral cavity. Patients were asked to point out any painful areas of their mouths to the researcher. This patient input was important as a previous study reported that patients are able to detect oral cavity changes between 1 day and 3 days earlier than Clinicians (Stiff et al., 2006).

7.6.2 Pain scores

The patient's reports of pain were collected using the Oral Mucositis Daily Questionnaire (OMDQ) (Stiff et al., 2006). A copy of this instrument can be found in Appendix 3. This tool was comprised of six questions and recorded patients' self reports of mouth and throat soreness, and diarrhoea events over the preceding 24 hours. This instrument also employed a skip pattern, allowing the patients to pass on questions that

did not apply. Baseline OMDQ assessments were conducted prior to randomisation and then daily until the patient met the exit criteria.

7.6.3 Nutritional screening

Patients underwent nutritional screening at baseline, prior to randomisation. This was repeated every seven days until the end of data collection. Patients were screened using the Patient Generated Subjective Global assessment (PG-SGA) instrument. This tool included the patient's medical history: weight changes, functional capacity, gastrointestinal symptoms, and dietary intake; an assessment of metabolic stress; and a short physical assessment to identify muscle wasting, oedema and loss of subcutaneous fat (Barbosa-Silva and Barros, 2006). A total score was then calculated.

Patients were asked to complete the first section of the form (patient medical history); however, in the event that the patient did not feel up to this task, the researcher asked them the relevant questions and completed this section for them. The researcher then calculated the patient's metabolic demands and performed the short physical assessment. The concurrent validity of the PG-SGA has been previously identified in populations with cancer and, as expected, was found to correlate with patient weight loss over the preceding 6 months (Bauer et al., 2002). The PG-SGA has also been reported to be a moderately reliable instrument (Bauer et al., 2002).

7.6.4 Researcher reflective diary

The researcher kept a reflective diary for the duration of the trial. This diary was used to record any issues and problems encountered during the trial, such as recruitment. This diary was used to complement the study data as an additional source of information while planning a larger full trial.

7.6.5 Definition of the end of the trial

The trial officially ended when the last visit was conducted with the last patient in the study. GB was responsible for notifying the LREC, MHRA and Sponsor of the end of the trial.

7.6.6 The patient journey

7.6.6.1 Allogeneic transplant

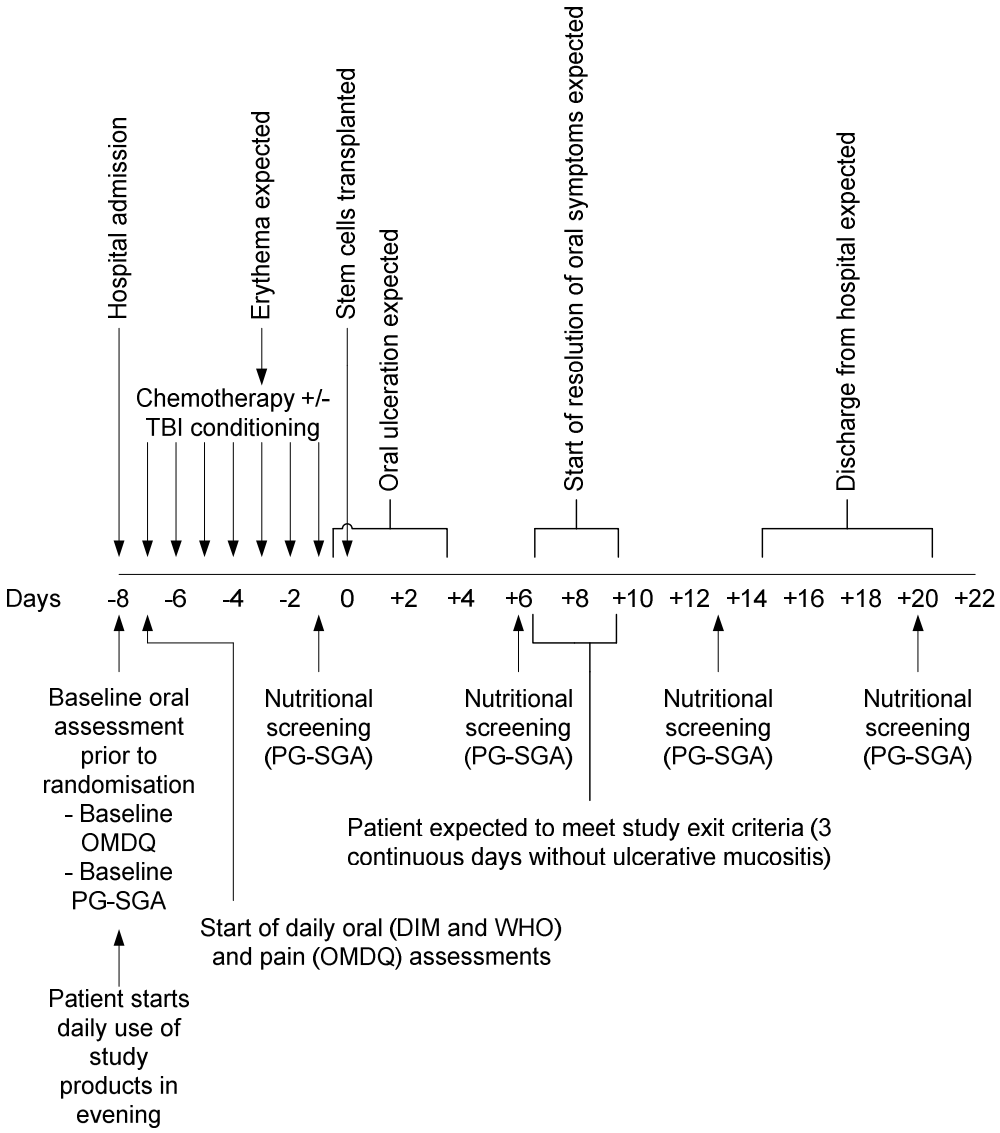


Figure 33: The Expected Journey of a Patient Undergoing Allogeneic Transplantation

Figure 33 shows the allogeneic patient experience. Patients undergoing allogeneic transplantation typically received seven days of conditioning before receiving their transplant. In addition to chemotherapy, this conditioning may also include TBI. Donated stem cells were administered to the patient, on their 9th day in hospital. This day is denoted ‘day 0’. The expected day of discharge for hospital varies depending on how well the patient coped with the transplantation process: whether they contracted a virus during hospitalisation or whether GVHD was a problem. Figure 33 also shows the patient experience during the feasibility study. It was planned that patients would

undergo baseline assessments prior to randomisation, on the day of their admission onto the unit. Oral (WHO, DIM) and pain assessments (OMDQ) would then be conducted daily and nutritional assessments weekly (PG-SGA). On the evening of the day of their admission into hospital, it was planned that patients would start taking the placebo or intervention products, and would continue to do so until they met the exit criteria for the study.

7.6.6.2 Autologous transplant

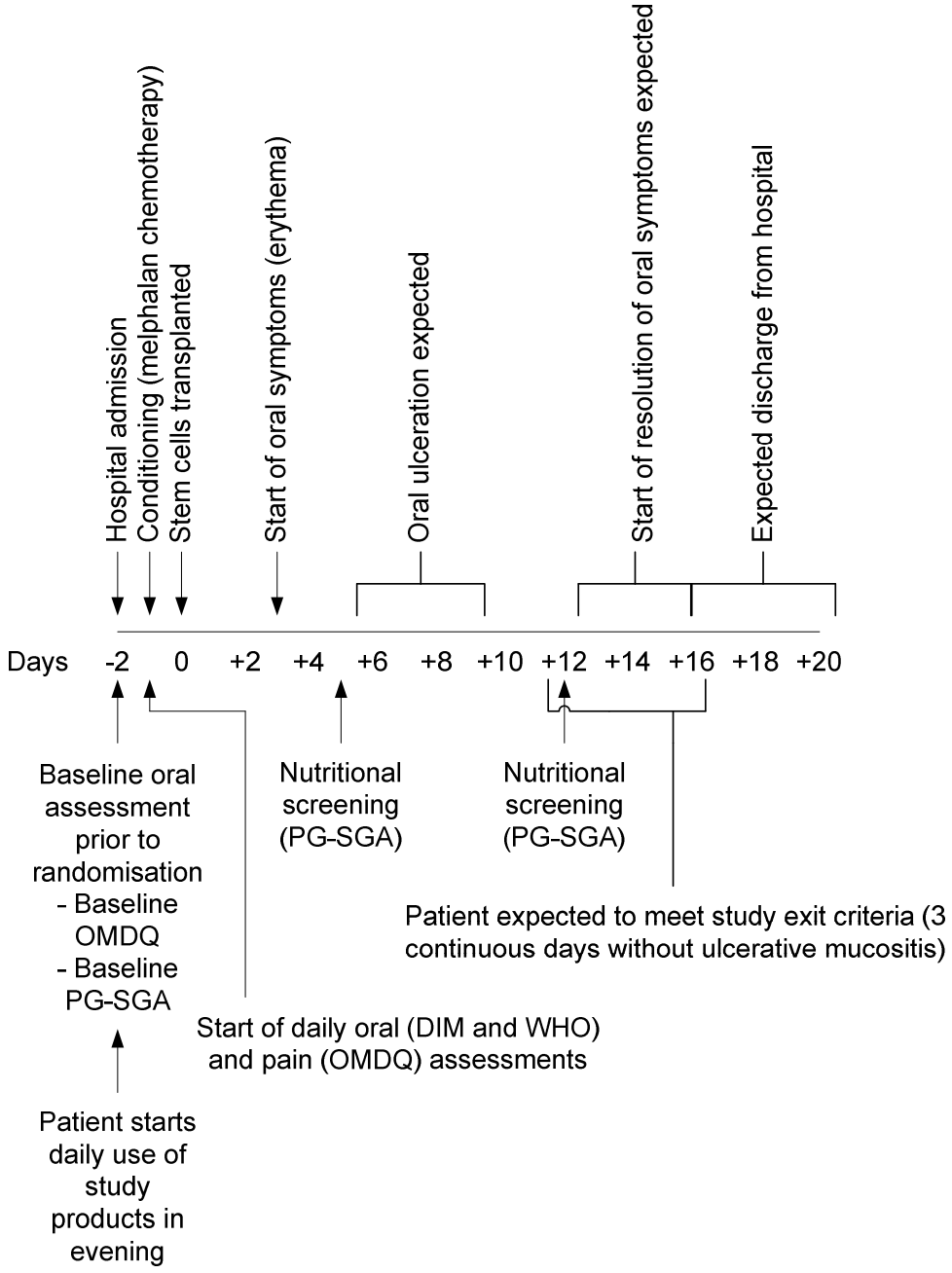


Figure 34: The Expected Journey of a Patient Undergoing Autologous Transplantation

Figure 34 shows the expected experience of patients undergoing autologous transplantation. Patients undergoing autologous transplantation typically received one day of conditioning, on the day after their admission to hospital. Their own harvested stem cells were administered on the day after conditioning, a day termed day '0'. The length of hospitalisation for autologous transplant patients was typically shorter than for allogeneic transplantation, but depended on how a patient coped with transplant. The patient experience during the feasibility study is also shown in Figure 34. Patients underwent baseline assessments prior to randomisation, on the day of their admission onto the unit. Oral (WHO, DIM) and pain assessments (OMDQ) were then be conducted daily and nutritional assessments weekly (PG-SGA). On the evening of the day of their admission into hospital, patients were asked to start taking the placebo or intervention products, and to continue to do so until they met the exit criteria for the study.

7.7 Pharmacovigilance

The recording of adverse events was an important part of the feasibility trial. Data were collected on all new events reported by a patient. The hospital standard operating procedures for the reporting of adverse events were followed, a copy of this document can be found in Appendix 7 (disk). As this trial was a feasibility study all adverse events were recorded, including all adverse events that are not considered to be urgent. The researcher was responsible for the safety reporting process. Data were collected on every new symptom experienced by the patient during the trial. Each new symptom was assessed using the criteria outlined in Table 14

Table 14: Adverse Event Reporting Definitions

	Definition
Adverse Event	"Any untoward medical occurrence in a patient enrolled in the study, who has been administered a medicinal product and does not necessarily have a causal relationship with this treatment"
Adverse Reaction	"All untoward and unintended responses to an investigational medicinal product related to any dose administered. All adverse events having a reasonable causal relationship to a medicinal product qualify as adverse reactions"
Unexpected Adverse Reaction	"An adverse reaction, the nature, or severity of which is not consistent with the applicable product information"
Serious Adverse Event or Serious Adverse Reaction (SAE or SAR)	"Any untoward medical occurrence or effect that at any dose which • results in death, • is life threatening, • requires hospitalisation or prolongation of existing hospitalisation, • results in persistent or significant disability or incapacity"
Suspected Serious Adverse Reaction	"A SSAR is defined as an SAR the nature and severity of which is consistent with information about the IMP in question as presented the investigator's brochure."
Suspected Unexpected Serious Adverse Reaction (SUSAR)	"Any SAR where the nature, or severity of the reaction is not consistent with the applicable product information in the investigator's brochure. **Requires expedient reporting to the MHRA and Trust and ethics committee."**

Adapted from the Hospital Standard Operating Procedures pages 5-7(see appendix 7)

7.7.1 Annual Safety Reports

The submitting of annual safety reports to the MRHA and the LREC was the responsibility of GB.

7.8 Statistics and data analysis

7.8.1 Plans for data analysis

Data were inputted by the researcher and a 10% sample was then double-checked. Data were analyzed using the Statistical package for the social sciences (SPSS) 15.0 and

Microsoft Excel. For the area under the curve analysis (AUC), missing data were generated by averaging the scores generated immediately before and after the gap. Data were analysed using the intention-to-treat principle (ITT). This allowed patients lost to follow-up, or who did not follow their randomized protocol to be analysed according to their randomised group. As this study was a feasibility study, the analysis was exploratory not hypotheses testing. It was planned that analyses would include confidence intervals and effect sizes in addition to point estimates, where possible. It was planned that the results of this feasibility study would be used to also provide figures that could be later used as the basis for sample size calculations for a larger study.

7.8.1.1 Primary analysis

The primary analysis compared AUC, for both the DIM and WHO scores, between the two treatment groups, based on the intention to treat principle. The Mann Whitney U test was used, and a 2-sided significance test was adopted with critical level of significance set at 0.05. This analysis was conducted by an independent statistician before the randomisation code was broken. The decision to use an independent statistician to conduct the primary analysis, and then break the randomisation code, was made by the researcher and her supervisors in an attempt to avoid the potential for bias. All other analyses were performed by the researcher.

7.8.1.2 Duration of ulcerative mucositis

The mean mucositis scores were determined for the intervention and control group for both of the oral assessment instruments. An area under the curve analysis was performed for these data to compare the two groups.

7.8.1.3 Highest DIM score

The mean daily index of mucositis scores was calculated for each of the two groups. An analysis was planned using the Mann-Whitney U test.

7.8.1.4 Highest WHO score

The mean daily index of mucositis scores was calculated for each of the two groups. An analysis was planned using the Mann-Whitney U test.

7.8.1.5 Nutritional screening

The highest nutritional score was calculated. An analysis was planned to compare the mean nutritional score at week three and the highest nutritional score by arm using the Mann-Whitney U test.

7.8.1.6 Pain scores

Analysis was conducted for each question on this instrument as the OMDQ did not require the calculation of a compound score. An analysis was planned using the Mann-Whitney U test.

7.9 Ethical issues

7.9.1 Confidentiality

The confidentiality of records that could identify participants were protected, and the privacy and confidentiality of patients was respected in accordance with the applicable regulatory requirements. Each patient enrolled in the study was given a patient number. Patient information was anonymised before being placed on university computers. Data held on external devices, such as pen drives, were anonymised and encrypted. Information sheets containing patient information was kept in a lockable filing cabinet.

7.9.2 Right to withdraw

Patients undergoing high dose chemotherapy or radiotherapy are obviously an at risk patient group. They therefore require treatment with sensitivity and support. The wishes of any participant who did not want to follow the study protocol on a particular day were respected. Patients who chose to withdraw from the study were respectfully asked if they would allow the researcher to follow them up by continuing to undergo daily oral and pain assessments and weekly nutritional assessments. Patients who declined were

thanked for their time and reassured that their withdrawal would not affect the standard of care that they would receive.

7.9.3 Consent

Obtaining adequate informed consent to participate in research is an important ethical issue. This feasibility study followed the guidelines pertaining to consent as outlined in the MRC guidelines for Good Clinical Practice in Clinical Trials (Medical Research Council, 1998)

7.9.4 Equipoise

There was genuine clinical equipoise: uncertainty whether a treatment would be of benefit (Freedman, 1987), in the feasibility trial because no ‘gold standard’ for the prevention of oral mucositis in patients undergoing conditioning for bone marrow transplantation currently exists, and previous trials of vitamin E for the prevention of mucositis have reported conflicting results.

7.10 Major conclusion

So far in this thesis, the mucositis literature and trials investigating interventions for the prevention of mucositis have been discussed and vitamin E has been identified as an intervention worthy of further study. The risk of bias in previously published trials has been investigated and using a sensitivity analysis, the importance of allocation concealment and outcome assessor blinding have been highlighted. How such trials can be used to inform future studies has been analysed, and the shortage of studies reporting adverse events has been discussed. A systematic review of oral assessment instruments has been also been presented, which has informed the choice of three assessment instruments. As shown in Figure 2, the results from these previous chapters have been used to inform the development of a protocol for use in a feasibility study which addresses all these issues. In the next chapter of this thesis the results of the feasibility study will be presented.

Chapter 8 Results of the Feasibility Study

8.1 Introduction

This chapter of the thesis presents the results of the feasibility trial and is split into two parts. The first section focuses on issues identified during the trial which may affect the feasibility of conducting a future study. The second section discusses the results of the study. Before going into detail about feasibility issues or the results of the trial, it is useful to be reminded of the previously stated study aim.

8.2 Aim

To explore the feasibility of conducting a trial to assess the effectiveness of d-alpha-tocopherol in the management of oral mucositis compared to a soya bean oil placebo, over and above standard care.

8.3 Section one: Feasibility

8.3.1 Regulatory requirements and pharmacy approval

Table 15 shows the timeline for gaining regulatory approval. The researcher first approached the hospital Research and Development (R and D) department in August 2007. At approximately the same time, the Medicines and Healthcare products Regulatory Agency (MHRA) was contacted to determine if the proposed trial necessitated MHRA approval. The MHRA application proved to be extremely time consuming and complex due to Healthplus not holding a manufacturers authorisation for an investigational medicinal product (MA-IMP). This necessitated a company with MA-IMP being contracted to repackage the products and for qualified person (QP) release. The same company (Preston Pharmaceuticals) also wrote the summary of product characteristics document necessitated for the MHRA application, which could not be supplied by Healthplus.

The MHRA application was initially refused, but was later accepted after the provision of additional product specification and sell-by date information from Healthplus and discussion between one of the researcher's supervisors and the MHRA. MHRA approval was granted on the 6th of June 2008 and the products were ordered from Healthplus the same day. The placebo was manufactured and was shipped from France

on 31st July 2008. Trust approval was finally received on 21st August 2008, having been held up by a delay in approval from the hospital pharmacy department. A further delay to starting the trial was caused by Preston Pharmaceuticals taking two months to package and release the products. The intervention and placebo products were eventually received by the hospital pharmacy on 6th October 2008, and the first patient started the trial on 28th October 2008. Table 15 shows the timeline for regulatory approval. From initial contact with the R and D department to the first patient starting the trial took 64 weeks.

Table 15: Timeline for Regulatory Approval

Date	Action
August 2007	Initial approach to hospital Trust Research and Development unit
	MHRA consulted to ask whether MHRA approval was necessary
September 2007	Preston pharmaceuticals contracted to repackage products and write IMPD document
October 2007	-
November 2007	-
December 2007	-
January 2008	-
February 2008	-
March 2008	Submission of initial MHRA application
	Submission of Ethics application
	Submission of Trust application
April 2008	Initial MHRA application rejected
	Resubmission of MHRA application
May 2008	-
June 2008	MHRA approval granted
July 2008	Placebo manufactured. Both placebo and intervention shipped to Preston Pharmaceuticals
August 2008	Trust approval granted
September 2008	-
October 2008	Intervention and placebo received by hospital pharmacy
	First patient enrolled
June 30th 2009	End of trial as sell-by date of intervention products reached

8.3.2 Clinician interest and available patient population

There are four consultant Clinicians on the BMT ward at the hospital, each with a different disease speciality. After initial contact with one of these Clinicians (EL), the researcher presented the project to all four consultants and the ward staff at a lunchtime education seminar at the hospital. During the presentation, one consultant voiced an objection to the planned number of patients to be recruited, stating that efficacy could not be proved with such small numbers across the three different types of transplant. When the researcher responded stating that exploration of feasibility issues was the primary aim of the study, the Clinician suggested the adoption of a phase 1 study in which all the patients were given the intervention of interest, and further stated that randomization and pharmacy release were unnecessary. Following discussion between the researcher's supervisors, and all four consultants, the Clinician in question refused to take part in the trial, denying the researcher access to his patients, which reduced the available patient population by approximately 33%.

After further discussions, an agreement was made between the supervisors and the remaining three consultants in order for the trial to go ahead, that instead of the patients swishing the liquid in their mouths and then swallowing, patients would be asked to swish and then expectorate the solution. The three consultants then agreed to take part in the study and allow the researcher access to their patients.

However, in the period running up to the recruitment of the first allogeneic patient, the consultant treating the autologous patients raised objections to the recruitment of allogeneic patients, despite confidence in the study of the consultant treating these patients, and stated that only his autologous patients should be recruited. This effectively forced the researchers and her supervisors to choose which consultant to work with; as two autologous patients had already started the trial, the decision was made to continue the study recruiting only the autologous patients. Unfortunately, these circumstances further limited the available patient population, as while the researcher was in theory working with two consultants, one of these doctors treated patients who were very rarely transplanted. This left the researcher recruiting only patients with multiple myeloma undergoing bone marrow and stem cell transplantation, a group of patients which comprised less than 25% of the available transplant population treated on the unit.

Attempts were made to increase pool of patients available to the researcher. The possibility of changing the study to incorporate a multi-site design and recruiting patients at a different hospital was explored, but rejected after an informal approach to clinicians on the relevant ward identified that this was not possible as the result of other trials occurring there. The inclusion criteria were also reassessed, but it was decided that changing them was not necessary as it was access to patients that was the problem, not a lack of patients who met the inclusion criteria.

8.3.2.1 Impact of the change in the method of application of the intervention and placebo

The change in the instructions to patients for the intervention and placebo products from 'swish and swallow' to 'swish and expectorate' had important consequences for the feasibility study. Firstly, it made determining what dose of vitamin E the patients actually received very difficult. It would be certainly less than the 670mg that they would have received had the vitamin E been swallowed, but the question of how much less could only be answered by a trial comparing the two methodologies. Measurement of plasma α-tocopherol levels are the easiest method of determining vitamin E levels in a patient (Olson, 2000). However, these were not measured in the feasibility study for two reasons: 1) such measures were not part of the routine blood tests and would have had to be specially requested from the laboratory, at considerable economic cost; and 2) as there was only one researcher collecting data, who was blind to the treatment allocation, the identification of changes in plasma vitamin E levels would have undermined outcome assessor blinding.

This swish and expectorate technique was also used in the Sung and colleagues trial (Sung et al., 2007), but the authors unfortunately do not comment on the possibility that the reason that no benefit of vitamin E was identified in their trial may have been due to the inactivity of vitamin E in the oral cavity. Neither do the authors comment on the decision making process that led to the products being expectorated instead of swallowed. As vitamin E can be absorbed through the skin (Wester, 2005), it stands to reason that it can also be absorbed through the oral mucosa or gingivae. However, at what rate this absorption takes place is unclear – the literature does not describe the rate of absorption in 5 minutes either through the skin, oral mucosa or gingivae – and it is

therefore unclear how much vitamin E could be absorbed in 5 minutes of swishing. The proposed mechanism of action for vitamin E in the prevention of mucositis has not been described, however, as previous studies asked patients to apply the intervention topically, by swishing before the solution was swallowed, it could be hypothesised that it was the local absorption of the product that is important, and not an effect on overall body status. It is very likely that some local absorption of the intervention took place during the five minutes of daily swishing undertaken by patients. However, researchers in future trials of vitamin E for the prevention of mucositis may like to reconsider how long patients receive supplementation. In the feasibility study, it was planned that patients would be supplemented for approximately 15 days. However, since studies have identified that it can take up to four weeks for plasma levels of vitamin E to become saturated, after supplementation with a daily dose of 900IU (Kitagawa and Mino, 1989), authors of future studies may like to consider a longer period of supplementation, if they consider that it is the whole body effect rather than any local effect that is the important mechanism of action for this intervention. In the same manner, if a whole body effect is hypothesised, patient use of supplements before recruitment may be important as depletion of vitamin E in adipose tissue is relatively slow and only takes place when plasma levels are low (Skeaff, 2007). Asking patients if they have previously used supplements, as was done is the feasibility study, is therefore advised.

8.3.3 Competing clinical trials

There were a number of clinical trials taking place on the unit during the data collection period. The majority of these trials compared survival outcomes in patients receiving different types of cancer treatments. None of these trials investigated interventions for the prevention or treatment of mucositis and there were therefore no competing clinical trials taking place during the data collection period. Two patients were enrolled in the myeloma X trial, a study investigating the use of a second autograft in relapsed patients who had previously received a stem cell transplant. However, Patient 9 withdrew from the myeloma X trial because he wanted to undergo another autograft and was unhappy with the possibility that he might be randomised to receive further chemotherapy treatment instead. Therefore, only one patient (Patient 6) was enrolled in another clinical trial at the time of entry to the vitamin E trial. This patient was allocated to the placebo group.

8.3.4 Feasibility of methods used to identify eligible patients

Eligible patients were identified at the weekly ward transplantation meetings, held on a Monday lunchtime. At this meeting the transplant co-ordinator presented patients being considered for transplantation over the next four to six weeks. Basic patient details including disease type, relevant co-morbidities, the date of the patient's next outpatient appointment and the name of their treating physician were provided during this meeting. Additional information about relevant patients was gleaned from discussions with the consultant treating the patient. With this information, the researcher was able to identify eligible patients to approach in clinic. This method of identifying patients was not foolproof, as patients were frequently moved on and off the transplantation list according to availability of beds, resulting in some patients being admitted for transplantation without ever appearing on the transplantation list.

8.3.5 Feasibility of Patient recruitment

Between October 2008 and June 2009, 22 patients were assessed for eligibility to enter the study. Two of these patients were not approached because of translation problems. Both patients required the involvement of translational services during clinic appointments, and while the patients could have been approached to take part in the study in the presence of a translator, due to staffing shortages, a translator would be unlikely to be available when the researcher returned to take consent, or during the daily data collection visits. Another two patients were assessed for eligibility but were not approached to take part in the study on the advice of the consultant Clinician. One of these patients had a history of non-compliance with treatment. The other patient had had a previous renal transplant, and it was medical consensus that this patient would have 'a difficult time'. Unfortunately, the patient in question died soon after transplantation.

Eighteen patients were approached to take part in the study. One patient originally approached when scheduled for an autograft went on to have an allograft, under the care of a consultant not taking part in the study. Another patient was approached but was not consented due to the use of warfarin. Seven patients refused to participate after being approached to take part in the study. Due to ethical restrictions, basic patient data were not collected on patients who refused to take part in the trial, and therefore comparisons cannot be made between patients who did and did not consent to take part in this trial.

Nine patients consented to take part in the trial and were randomised. Recruitment stopped on June 30th 2009, when the sell-by date for the intervention was reached. The possibility of purchasing additional Vitamin E and extending the study was followed up on; however the time required for Ethics, MHRA and Trust approval for an extension to be granted, and to permit the production of this thesis within the University of Manchester's time requirements, meant that this was not considered feasible.

Figure 35 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram showing the recruitment of patients into the study.

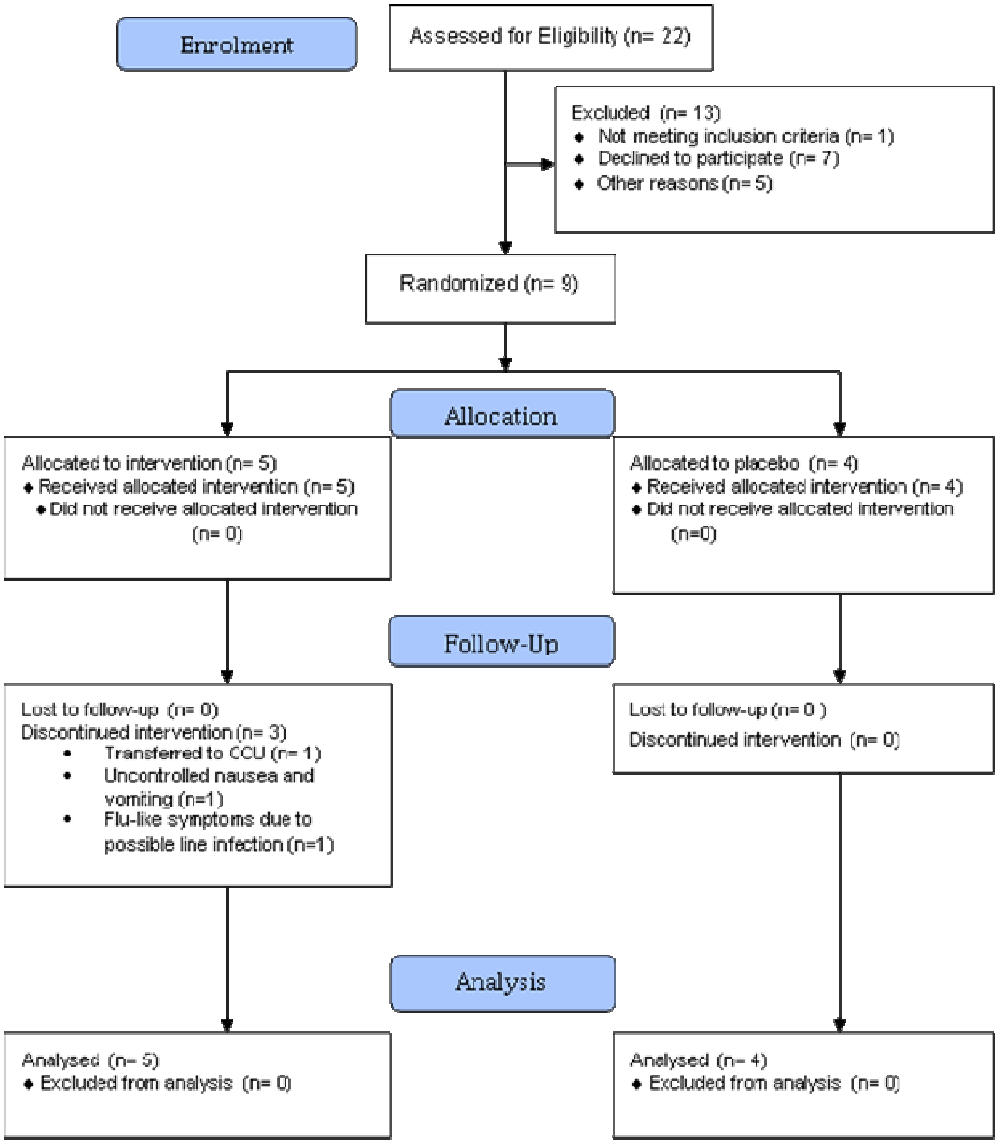


Figure 35: CONSORT Diagram Showing Recruitment and Follow-up of Patients and Data Analysis

8.3.6 Feasibility of the informed consent, randomisation and pharmacy release procedures

The Ethics Committee mandated that all patients should be approached in the presence of a medical professional. While this was achievable in the outpatients' clinic, where introductions were made by the consultant Clinician or a specialist registrar, recruitment of patients elsewhere in the hospital was difficult to organise and often poorly executed. In such circumstances the researcher was introduced to the patient by a nurse, who was often not aware of the project and who had also not previously met the patient. This meant that a considerable amount of researcher time was spent arranging to be introduced to the patient and then waiting for this introduction to be made. In one instance, the researcher spent four hours on the ward waiting for a nurse to be available to introduce her to the patient.

Of the 18 patients approached to take part in the study, 14 were approached in the Myeloma outpatient clinic and seven of these patients consented to take part in the study. Two patients were missed in the clinic and were approached when they attended the day ward for blood tests. Both patients consented to take part in the study and both were randomised to the placebo group. The final two eligible patients were approached on the ward after they were admitted for their autograft. Neither of these patients consented to take part in the study, with one patient commenting that the trial was something they would have been interested in taking part in, however, since arriving on the ward the enormity of the transplantation procedure had left them unable to comprehend taking part in anything else; had they heard about the trial before hand they would probably have been willing to consent to taking part. While it is likely that circumstances may dictate the need for patients to be approached after being admitted to the ward or in other areas of the hospital; the recruitment of patients in outpatient clinics where the researcher can be properly introduced to the patient and the aims of the project clearly laid out appears to be the best strategy in future trials.

All patients recruited to the study were consented on the ward on the day of admission for transplant. This proved to be problematic. The majority of patients were admitted onto the ward late in the afternoon and the researcher found that she was competing with the medical staff for time with the patient. After informed consent was obtained the patient was assigned the next available sequential patient number and the pharmacy release form was completed. This form required the signature of a doctor. As senior

house officers rotated twice during the data collection period of this study, this signature sometimes took a while to achieve because a new rotation of doctors had to be informed about the study before a signature was requested. After the form was completed it was given to the ward pharmacist who delivered it to the pharmacy. Occasionally, the ward pharmacist would fill this prescription himself, ensuring that the capsules were being delivered to the ward before the researcher left for the day. If the ward pharmacist was busy the prescription was filled by the duty pharmacist and would therefore arrive on the ward with the evening drug delivery, at approximately 8pm. When drugs were arriving in the evening the researcher had to determine which nurse would be responsible for the patient, find them and ask them to give the capsules to the patient once they arrived on the ward. Most of the time this worked well, however, patient 7 missed her first dose of the drug because the drugs were delivered to her room and then immediately placed in the locked box next to her bed.

While it was possible to consent a patient, gain relevant signatures, organise pharmacy release and enrol the patient in the trial, on both the electronic system and in their paper notes, in the three or so hours between the patient being admitted on to the ward and the pharmacy closing for the day at 5pm, it made for an extremely busy afternoon. No two patients were enrolled into the study on the same day. However, as many as three eligible patients were admitted to the ward at the same time. In this instance, had all three patients consented to take part in the study, completing all the consenting and enrolment procedures in the time allowed would not have been feasible, resulting in some patients starting a day later than planned. During the design of this study it was envisioned that patients would receive their first dose on the day prior to receiving chemotherapy. It should be noted that there was no scientific basis for the recruitment of patients on the day of admission, however for the consistency of the results it is advisable that patients are recruited no later than the day on which they begin their chemotherapy, in order to ensure that the first dose of the intervention is administered at a similar stage of their treatment.

8.3.7 Feasibility of adverse event reporting

Adverse events were recorded daily and graded using the CTCAE version 3, an extensive whole body grading system which is commonly used to grade adverse events in clinical trials involving patients with cancer. Adverse events assessed as serious (grade 3 or above) – and were therefore considered life threatening or which could

result in prolonged hospitalisation – were assessed for causality (using five categories: not related, unlikely, possibly related, probably related, definitely related) to the study products by the researcher and the patient's consultant using the hospital pharmacovigilance guidelines (appendix 7). This method of assessing adverse events was included in the study protocol and discussed with the research ethics committee (REC) in person at the REC meeting.

Before data collection started the researcher was unsure what the common side effects associated with stem cell transplant would be. Therefore the decision was made to collect data on every adverse event experienced by the patients during the study. This proved to be very time consuming for the researcher, necessitating accessing three different sets of notes for each patient all stored in separate parts of the ward. Adverse event reporting was estimated to take the researcher an hour a day for each patient taking part in the study. As the average of days a patient was on the study was 16, this equated to 16 hours of adverse event reporting per patient, or 144 hours (or 18 working days) overall. However, while prospective adverse event reporting was extremely time consuming, these data can be used to inform researchers in designing a future protocol in this field.

8.3.8 Feasibility of blinding and allocation concealment

The randomisation sequence was concealed by the use of sequentially numbered containers which were identical in appearance which were released by the pharmacy upon receiving the completed pharmacy release form. Copies of the randomisation sequence were held by the researcher's PhD supervisors, the pharmacy and the consultant whose patients were recruited. An initial suggestion by the consultant of placing a copy of the sequence in the site study file was rejected by the researcher and the supervisors on the grounds that this file was not secure, and could be opened by anybody on the ward. All data were entered and the AUC analysis conducted before the randomization code was broken.

Both patients and the researcher were blind to the treatment allocation. Because of the possibility of slight colour variation between the two different types of capsules, the researcher organised for the departmental pharmacist to check compliance to the study

protocol by counting the capsules in each returned pot when the patient exited the study. The pharmacist then returned the pot to the pharmacy for disposal and communicated only the number of capsules to the researcher. As allocation concealment was maintained during the study, in addition to the researcher and the patient, the nursing staff caring for the patient were blind to whether the patient was receiving the intervention of interest or placebo.

8.3.9 Substantial amendment

It was originally stated in the protocol that in the event of a SUSAR patients currently enrolled in the study would be informed and re-consented. However, during the course of data collection it became clear that this would require amending. One of the patients who declined to take part in the study later developed pancreatitis and narrowly escaped an admission to CCU, which had he been enrolled in the trial would have been classified as a SUSAR, necessitating expedient reporting to the MHRA and the ethics committee. This is such an atypical complication that, had this patient been enrolled in the study, determining causality to the intervention or placebo would have been difficult, resulting in the SUSAR being erroneously classified as 'possibly' due to the intervention or placebo due to the rarity of such a side effect. Therefore, it was decided that in the event of a SUSAR only those events assessed as being 'probably' or 'definitely' related to the intervention or placebo would require patients to be informed and re-consented. SUSARs assessed as being possibly due to the intervention or placebo, but could just of likely resulted from something else would not require patient re-consent. The application for the substantial amendment was made on 30th January 2009. Approval from the MHRA was received on 25th March 2009. The project continued using the original SUSAR rules during this time and changed to the new rules once all approvals had been received.

8.3.10 Compatibility of clinical trial with standard care

This trial was designed to be conducted over and above standard care for mucositis. However, the Haematology ward did not have a formal intervention for mucositis prevention or treatment, and an *ad hoc* approach to prescribing based on Clinician preference had been adopted. Therefore Table 16 shows a variety of different interventions prescribed for the management of mucositis.

Table 16: Other Treatments Employed for Mucositis

	Intervention	Placebo	Total
Cryotherapy	2	0	2
Difflam	2	2	4
Gelclair	0	1	1
Saline Mouthwash	2	1	3
Salt and Soda Mouthwash	1	0	1
Synthetic Saliva	1	1	2
None	1	0	1

No patients were prescribed any intervention to *prevent* mucositis. However, one patient (Patient 3: intervention) had read about the benefits of cryotherapy on the internet and had sucked ice-pops during melphalan infusion. Another patient (patient 5: intervention) was given an ice-pop and a glass of iced water during melphalan infusion by a nurse who had read the Cochrane Review on the prevention of mucositis (Worthington et al., 2007).

8.3.11 Conclusion for section one

The first section of this thesis chapter has focused on feasibility issues identified during the trial. This feasibility trial suffered from delays in ethical approval and in the packaging of the intervention and placebo products. Difficulties gaining access to potentially eligible patients together with low rates of patient recruitment resulted in only nine patients being recruited into the trial before the trial closed in June 2009, when the sell-by date for the intervention products was reached. Routine oral care was not standardized on the unit, which resulted in a wide range of products being prescribed to patients. These issues will be addressed in the discussion chapter.

8.4 Section two: Results

8.4.1 Patient characteristics

Of the nine patients recruited into the study, five patients were randomly allocated to the intervention arm. The remaining four patients were allocated to receive the placebo. Table 17 details which patients were allocated to each arm.

Table 17: Randomisation of Patients to the Intervention and Placebo Arms

Placebo	Intervention
Patient 1	Patient 2
Patient 4	Patient 3
Patient 6	Patient 5
Patient 7	Patient 8
	Patient 9

Table 18 displays the characteristics of the patients who consented to take part in the study. All patients had a diagnosis of multiple myeloma. A variety of different types of myeloma were represented. One patient had non-secretory multiple myeloma, a rare form of the disease. Five of the nine patients recruited were male (56%). The mean age of the patients in the intervention group was 54.40 years old (SD=5.320). The youngest patient recruited in the study was 46 years old, and was randomised to receive the intervention. This patient had received previous radiotherapy for a testicular carcinoma in 2000. One placebo patient had also previously received radiotherapy to his pelvis during earlier myeloma treatment (Patient 6). All patients received melphalan in a dose of 200mg/m^2. As this dose is calculated based on body surface area (BSA), and the patients in the intervention arm were heavier, it is not surprising that the mean dose of melphalan received by patients in the intervention arm was higher than that received by patients in the placebo arm. All patients had experienced prior chemotherapy, with two patients, one from each arm, having had a previous autologous transplant.

There was large amount of variation in the amount of stem cells patients received. The mean overall stem cell dose was $3.80x10^6$/kg. The intervention group received a substantially lower dose of stem cells than the placebo group. Patient 6 (placebo) received $13.62x10^6$/kg stem cells. This exceptionally high dose was due to an extremely high collection being frozen for preservation during his previous transplant. As the bag of cells had been frozen it was not possible to split the collection into smaller doses. If the cell collect of Patient 6 is excluded, the placebo group received a mean of $3.32x10^6$/kg, still larger than the intervention group mean of $2.12x10^6$/kg. One patient (Patient 9: intervention) received a combination of stem cells and bone marrow. Three patients recruited into this study were ex-smokers. All three stated that they had previously smoked less than a packet of cigarettes a day.

Table 18: Baseline Characteristics

Variable	Category	Intervention (n=5) (%)	Placebo (n=4) (%)	Total (n=9) (%)
Gender	Male	3	2	5
	Female	2	2	4
Age (years)	Mean	54.40	54.75	54.56
	Range	46-60	52-57	46-60
	SD	5.320	2.630	4.096
Height (cm)	Mean	169.68	170.35	169.98
	Range	152-183	156-185	152-185
	SD	15.55	12.26	13.32
Weight (kg)	Mean	95.7	82.6	89.9
	Range	75.0-106.8	70.0-88.5	70.0-106.8
	SD	12.34	8.654	12.32
BMI (kg/m^2)	Mean	33.46	28.80	31.39
	Range	29.9-41.6	25.1-36.4	25.1-41.6
	SD	4.6998	5.2339	5.2296
Melphalan dose (mg/m^2)	Mean	420	380	402.2
	Range	360-460	360-400	360-460
	SD	40.0	23.09	38.0
Cells ($x10^6/kg$)	Mean	2.12	5.89	3.80
	Range	2.03-2.24	2.45-13.62	2.03-13.62
	SD	0.08	5.20	3.76
Previous Chemotherapy Regimes	CTDx6	3 (33.3)	2 (22.2)	5 (55.5)
	VADx6	1 (11.1)	0 (0)	1 (11.1)
	CTDx2/VEL DEXx2	1 (11.1)	0 (0)	1 (11.1)
	CD/CVADx3/PADx2	0 (0)	1 (11.1)	1 (11.1)
	CZDEX x4, PADx2	1 (11.1)	0 (0)	1 (11.1)
Previous Auto		1 (11.1)	1 (11.1)	2 (22.2)
Previous Radiotherapy		1 (11.1)	1 (11.1)	2 (22.2)
Type of Multiple Myeloma	Light Chain Myeloma	0 (0)	2 (22.2)	2 (22.2)
	IGG (Kappa) Myeloma	1 (11.1)	1 (11.1)	2 (22.2)
	Non-secretory Myeloma	1 (11.1)	0 (0)	1 (11.1)
	Oligosecretory Myeloma	2 (22.2)	0 (0)	2 (22.2)
	IGA Myeloma	1 (11.1)	1 (11.1)	2 (22.2)
Medical History	Testicular cancer	1	0	1
	Sleep Apnoea	1	0	1
	Barretts's Oesophagus	1	0	1
	Leg Ulcer	0	1	1
	DVT	0	1	1
Medical History (Cont.)	IBS	1	0	1
	Asthma	1	0	1
	Breast cysts	0	1	1
	Gynaecological polyps	0	1	1
	Jugular thrombosis	0	1	1
Smoking	Never	3 (33.3)	3 (33.3)	6 (66.6)
	Former	2 (22.2)	1 (11.1)	3 (33.3)

CTD= Cyclophosphamide, Thalidomide and Dexamethasone. **VAD**=Vincristine, Adriamycin and Dexamethasone. **VEL DEX**=Velcade, Dexamethasone. **CD**= Cyclophosphamide, Dexamethasone. **CVAD**= Cyclophosphamide, Vincristine, Adriamycin and Dexamethasone. **PAD**= Bortezomib, Doxorubicin and Dexamethasone. **CZDEX**=Cyclophosphamide, Idarubicin and Dexamethasone.

Three patients did not complete the study. One patient (Patient 2: intervention) was withdrawn from the study at day+9 due to her urgent admission to the CCU with a chest infection. Two patients discontinued the intervention after 5 days of supplementation (Patient 8) and one day of supplementation (Patient 9) respectively. Both these patients were randomised to receive the intervention. Patient 8 withdrew from the study due to uncontrolled nausea and vomiting. Patient 9 withdrew due to rigors and flu-like symptoms that were due to a suspected infection in his Hickman line. These symptoms ceased after the line was removed. Both patients gave verbal consent for the researcher to continue to collect daily oral and pain, and weekly nutritional scores after they stopped supplementation. It was the opinion of the consultant Clinician that neither patient's symptoms were due to the intervention.

8.4.2 Adherence patterns

Based on previous reports of the duration of mucositis, it was thought that patients would receive the intervention or placebo for approximately 15 days. This was a correct estimation for the patients in the placebo arm. Table 19 shows the mean, median, range and standard deviation (SD) of supplementation for both groups.

Table 19: Days of Supplementation

Variable	Intervention	Placebo	Overall
Mean (doses)	7.20	15.0	10.67
SD	2.11	1.29	5.52

The highest number of doses received was 18 (Patient 6). This patient missed three doses on day+1, day+12 and day+15. When this patient missed his first dose, he took two doses the next day (morning and evening). He was counselled not to do this again. The lowest number of doses received was one (Patient 9). This patient suffered from flu-like symptoms during administration of chemotherapy and stem cells and withdrew from the study. Four patients missed their first dose of the medication. Patient 7 (placebo) missed the first dose due to a staff error (see feasibility of informed consent, randomisation and pharmacy release). Patient 8 (intervention) was admitted to the ward on the day of his melphalan infusion (day-1) due to a lack of beds. Patient 5 was admitted to the ward with a slight cough, his first dose was therefore omitted because the decision of his suitability for transplant was delayed until the following morning. Patient 9 (intervention) was also admitted on the day his chemotherapy was due,

resulting in the first dose being missed. This patient then missed his second dose due to the aforementioned flu-like symptoms. The patient who missed the most doses was patient 4 who missed seven doses. This was partially due to the patient going to sleep very early in the evening, and therefore being unable to take her placebo dose last thing in the evening. After discussion with the researcher she tried taking her capsule in the afternoon. However, this was not too successful as she subsequently became ill with febrile neutropenia and missed more doses.

8.4.3 Withdrawals

Table 20 shows patient withdrawals from the trial. Three patients withdrew from the study. All three of these patients were randomised to receive the intervention. Patient 2 was admitted to the CCU on day+8 after receiving 9 days of supplementation. Patient 8 withdrew due to uncontrolled nausea and vomiting on day+2 after receiving four doses of vitamin E. Patient 9 also withdrew due to flu-like symptoms and rigors which required oxygen supplementation. This patient had been on the study for three days but had only received one dose (on day 0). The mean doses for the intervention group shown in Table 19 do not reflect either the three patients who missed their initial dose or the three patients who withdrew from the study in this group.

Table 20: Reasons for Withdrawals

Reason for withdrawal	Intervention	Placebo
CCU admission	1	0
Flu-like symptoms and rigors	1	0
Uncontrolled nausea and vomiting	1	0
Total	3	0

8.4.4 Patterns of mucositis

Due to the low number of patients recruited to take part in this study it is unwise to discuss any differences between the study arms, as such differences are likely to be a Type II error. Therefore the focus of the next section will not be on statistical differences between the groups, however, the results of individual patients will be discussed.

8.4.4.1 Area under the curve

Table 21 shows the area under the curve analysis for the two arms of the study. This analysis was conducted by a Statistician blinded to the randomisation key. The randomisation key was broken only after all data had been entered and the primary analysis had been conducted.

Table 21: Area under the Curve Analysis for Days +1 to +15.

	N	Mean	SD	Test statistic	df	p	95% CI for difference	Effect size
DIMcombined								
Placebo	4	303.0	52.2	t=0.48	6	0.646	-72.1 to 107.6	d=0.34
Intervention	4	285.3	51.6	Z=-0.58		0.686		r_Z=0.20
WHOscore								
Placebo	4	18.1	11.1	t=0.25	6	0.810	-14.2 to 17.4	d=0.18
Intervention	4	16.5	6.6	Z=-0.15		0.886		r_Z=0.05

$$AUC = (x2 + x1)/2 + (x3 + x2)/2 + \ldots + (x15 + x14)/2$$

$$= \sum xi - x1/2 - x15/2$$

where $\sum xi$ is the sum over all of x1, x2, …, x15.

Equation 1: Area under the Curve (AUC)

The AUC was calculated using the equation shown in Equation 1. Patient 2 was excluded from the analysis due to the extent of the missing data for this patient. A small number of missing values were substituted to obtain complete values for the remaining 8 participants using linear interpolation for missing observations before day 15 (4 observations out of 60 for DIMcombined and 1/60 for WHOscore) or last observation carried forward for day 15 (one observation for each measure). As expected with such a small sample, Table 21 shows no significant differences between the arms for mucositis measured using both the DIM and WHO instruments.

8.4.4.2 Duration of ulcerative mucositis

Table 22 shows the duration of ulcerative mucositis as measured using the WHO tool. The placebo group experienced both a higher mean and median duration of mucositis. This may be due in part to patient 6 suffering with ulcerative mucositis for 11 days.

Table 22: Duration of Ulcerative Mucositis Measured Using the WHO Instrument

Variable	Intervention	Placebo	Overall
Mean duration (days)	4.60	6.25	5.33
SD	4.57	2.61	3.46
Median (days)	3.00	7.00	5.00

8.4.4.3 Highest WHO mucositis grades

Table 23 shows the highest mucositis grades experienced by patients during the trial. One patient (patient 7) did not develop ulcerative mucositis, represented by a WHO score greater than 1. Two patients (Patients 1 and 9 respectively) developed ulcers but did not report problems swallowing solid food. Patient 8 was the only patient to develop a mucositis score of four due to a bleeding ulcer at the back of his throat that inhibited drinking solids and made swallowing painful. However, with adequate pain control this situation lasted only 24 hours.

Table 23: Highest Mucositis Grades Measured Using the WHO Instrument

Arm	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Total
Intervention	0	0	1	3	1	5
Placebo	0	1	1	2	0	4
Total	0	1	2	5	1	9

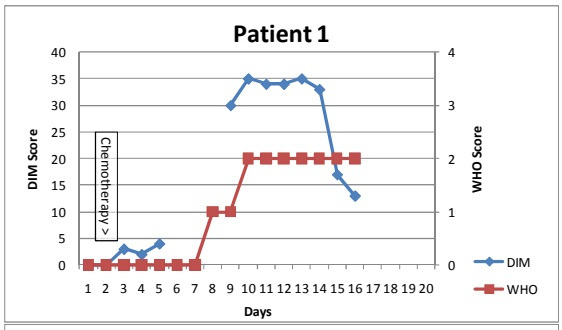
8.4.4.4 Mean mucositis scores measured using the DIM tool

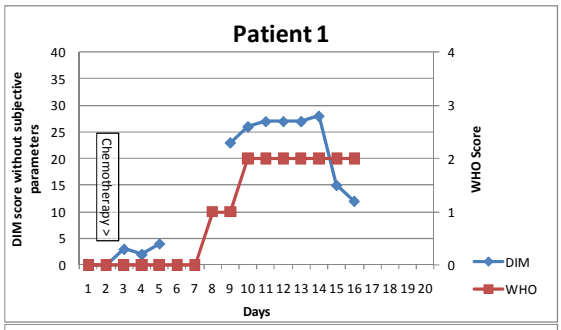
Table 24 displays the mean and the median Daily Index of Mucositis scores for each arm. The intervention group experienced a lower mean but a higher median DIM score. This group also had a much larger standard deviation possibly due to Patient 9 (intervention) only experiencing a maximum DIM score of 24 and Patient 8 (intervention) and Patient 2 (intervention) experiencing scores of 38 and 39 respectively.

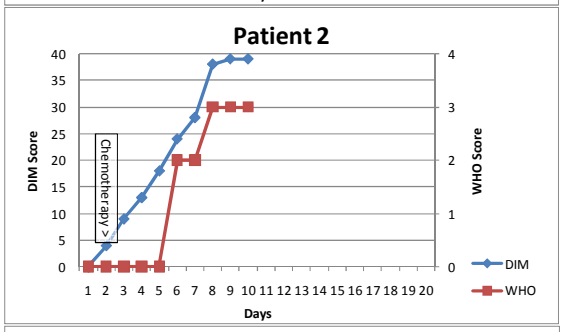
Table 24: Mean Mucositis Scores Measured Using the DIM Instrument.

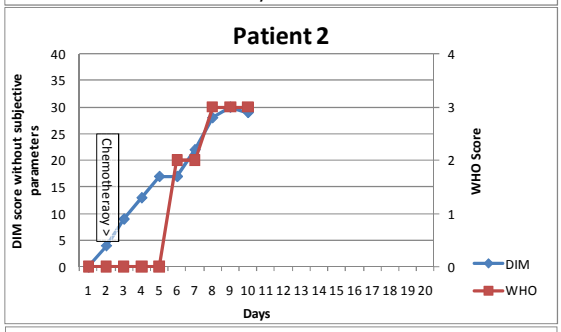
Variable	Intervention	Placebo	Overall
Mean score (DIM)	33.00	33.75	33.3
SD	6.04	3.50	4.80
Median (DIM)	35.00	33.50	35.0

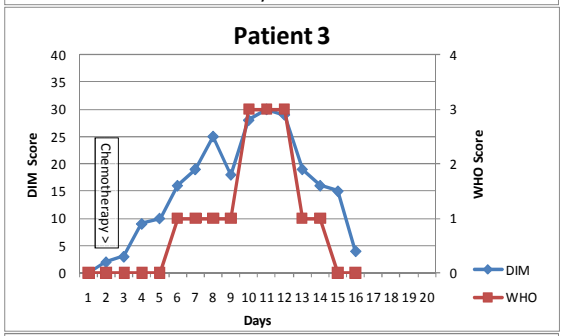
8.4.4.5 Comparison of DIM scores to WHO scores

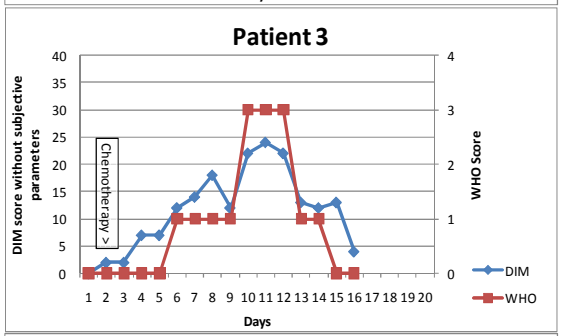


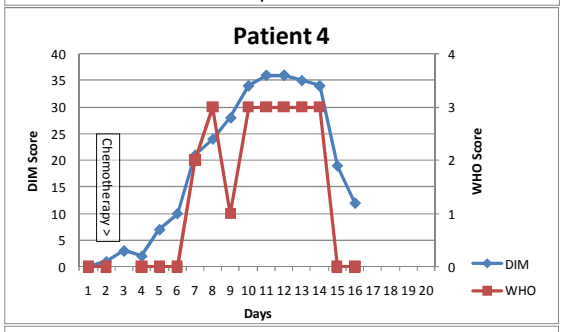


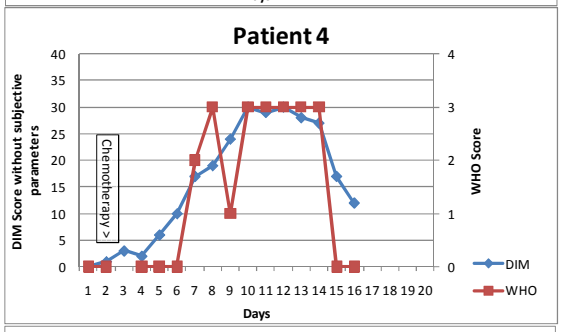


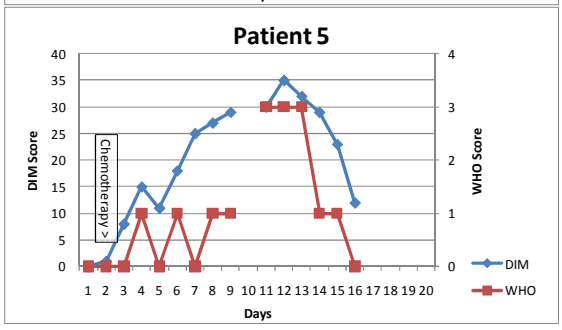


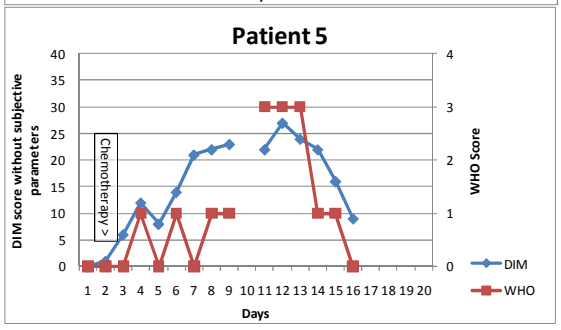












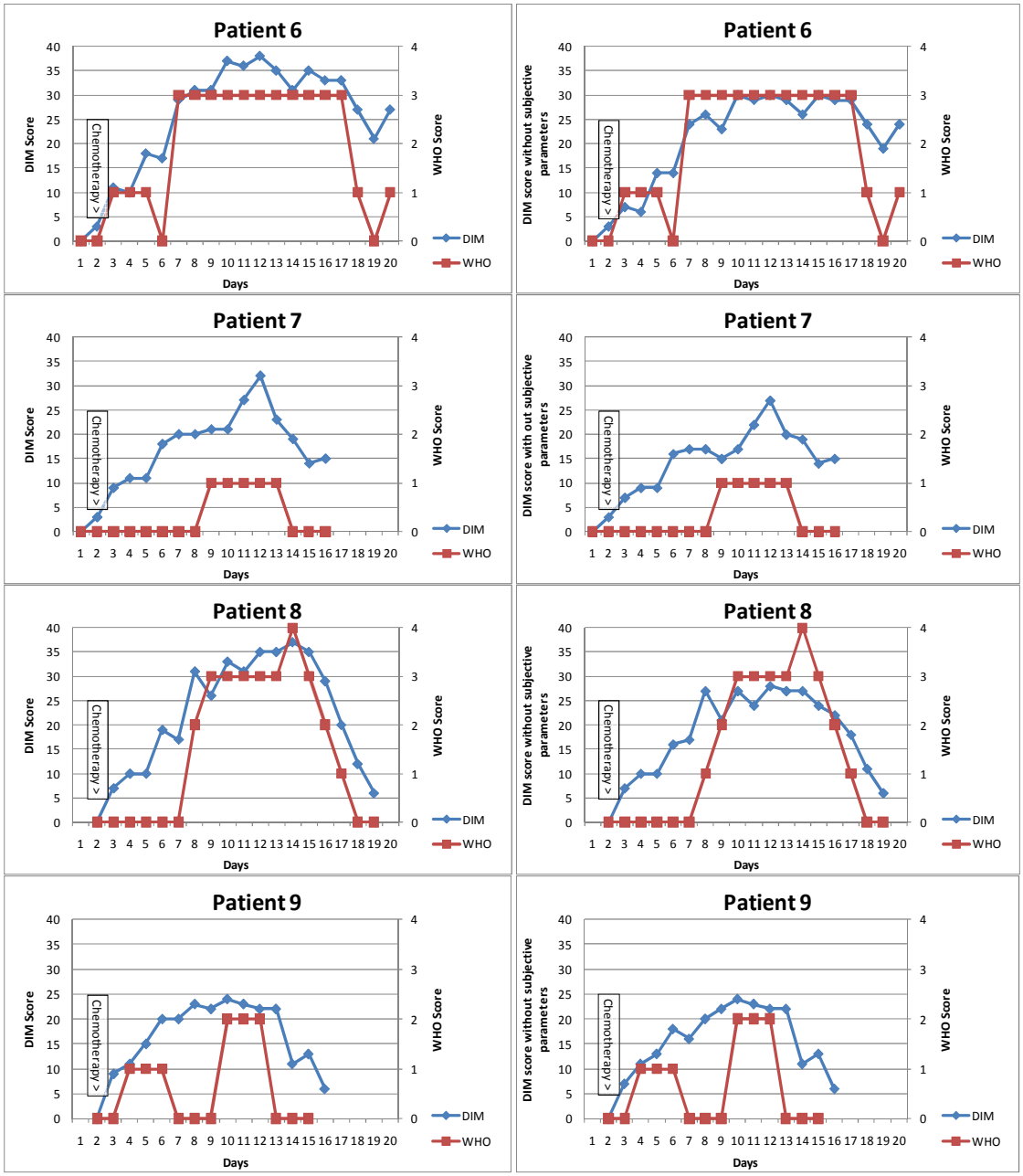


Figure 36: Comparisons of DIM Score and DIM Score Without Subjective Parameters With WHO Score[34]

In order to explore the differences between the oral assessment instruments graphs comparing the WHO and DIM daily values were plotted for each patient (Figure 36). As the DIM instrument was designed to allow for the exclusion of subjective assessment parameters (pain, talking, saliva, swallow), an altered DIM score was also plotted against the WHO results for comparison. Overt differences can be seen between the oral assessment instruments for three patients. The WHO score for Patient 1 indicates that

[34] DIM assessed from zero (none) to 40 (worst possible grade), WHO score assessed from zero (no mucositis) to four (severe mucositis)

this patient was still ulcerative at discharge from hospital. However, the DIM instrument indicates a substantial improvement in the patient's condition in the previous four days, represented by a considerable decrease in score (from 35 to 13). This pattern remains similar when the subjective elements of the DIM instrument are removed.

The WHO score for Patient 6 suggests that the oral condition in the patient is getting substantially better, however, the results of the DIM instrument are still extremely high, and are not greatly changed by the removal of the subjective components of the instrument. In the graphs for Patient 7 the DIM instrument once again indicates that the patient's oral problem has not resolved. The differences between the WHO and DIM instruments results are not explained by the removal of the subjective parameters from the DIM tool in any of the nine patients recruited into the trial. It is clear that the DIM instrument provides more information about the condition of the oral cavity than the WHO instrument. However, it is considered worthwhile to also utilise the WHO scale in a clinical trial as it permits data to be dichotomised in a meta-analysis. Currently, the inclusion of multi-component instruments (such as the DIM instrument) is not usually possible in a meta-analysis due to the complexity of dichotomising data across a variety of instruments which have a large variation in total scores. As such, use of the DIM score alone could mean the exclusion of any study from future meta-analyses. Adoption of the WHO scale therefore permits greater comparability with other studies, at the cost of relatively minimal additional researcher work, and no additional patient burden.

8.4.5 Pain

Patients were asked to complete the Oral Mucositis Daily Questionnaire (OMDQ) once daily during supplementation. This instrument is comprised of six questions and asks patients to rate their overall health (scored from one: 'worst', to ten: 'perfect', on a VAS), the amount of mouth and throat soreness they have experienced over the preceding 24 hours (scored from zero: 'none', to four: 'extreme'), and the impact such soreness has made on their ability to swallow, drink, ear, talk and sleep (scored from zero: 'none', to four: 'unable to do'), their overall mouth and throat soreness during the preceding 24 hours (scored from one: 'none', to ten: 'worst', on a VAS), the amount of diarrhoea they have experienced (scored from zero, none, to four, severe) and rate the severity of this diarrhoea (scored from one: 'none', to ten: 'worst', on a VAS). One

patient (Patient 2, intervention) failed to complete the questionnaire twice while suffering from uncontrolled nausea, vomiting and diarrhoea. All remaining patients completed the questionnaire every day during supplementation. The results of each question will now be discussed in the order in which they were asked.

8.4.5.1 Overall health

Placebo | Intervention

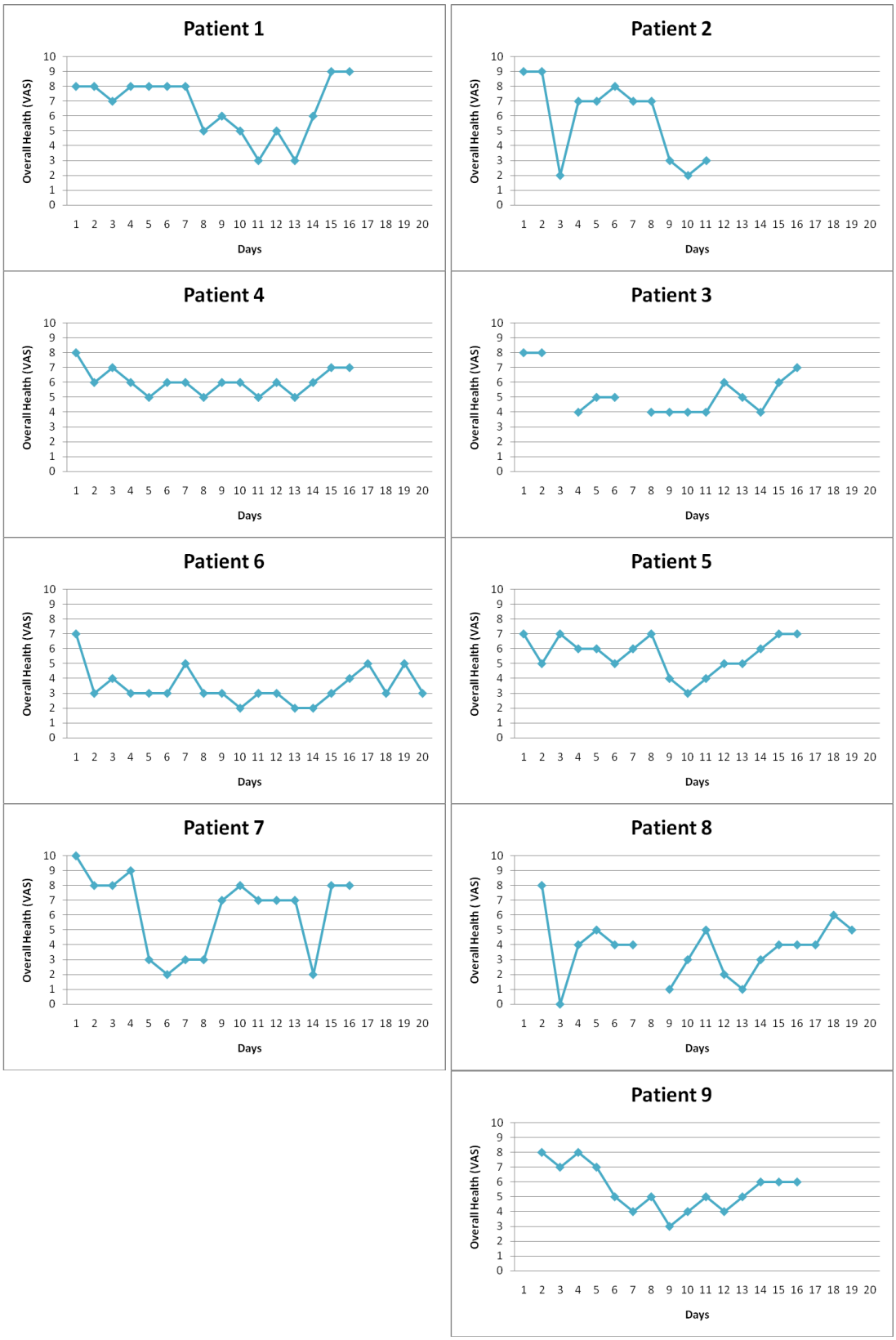


Figure 37: Patient Assessments of Overall Health Plotted Against Time[35]

[35] Score of 10 indicated best possible health, score of 0 indicated worst possible health

Figure 37 shows the patients' perception of their overall health in the previous 24 hours. At baseline this question commonly provoked the response "I've got cancer". In this instance the researcher tried to get the patient to focus on the previous day, and not on their diagnosis, unless this had been a problem within the last 24 hours.

All patients experienced a decrease in their perception of overall health at some point during treatment. The greatest decrease from baseline in overall health reported was a decrease of eight on the VAS. This was seen in two patients (Patients 8 and 9 respectively). The lowest drop in perception of overall health was reported by Patient 4 (placebo), who reported a decrease of 3 on the VAS. Only one patient (Patient 8: intervention) reported a score of zero (worst possible). This was on day+1, 48 hours after receiving chemotherapy.

8.4.5.2 Mouth and throat soreness in previous 24 hours

Placebo Intervention

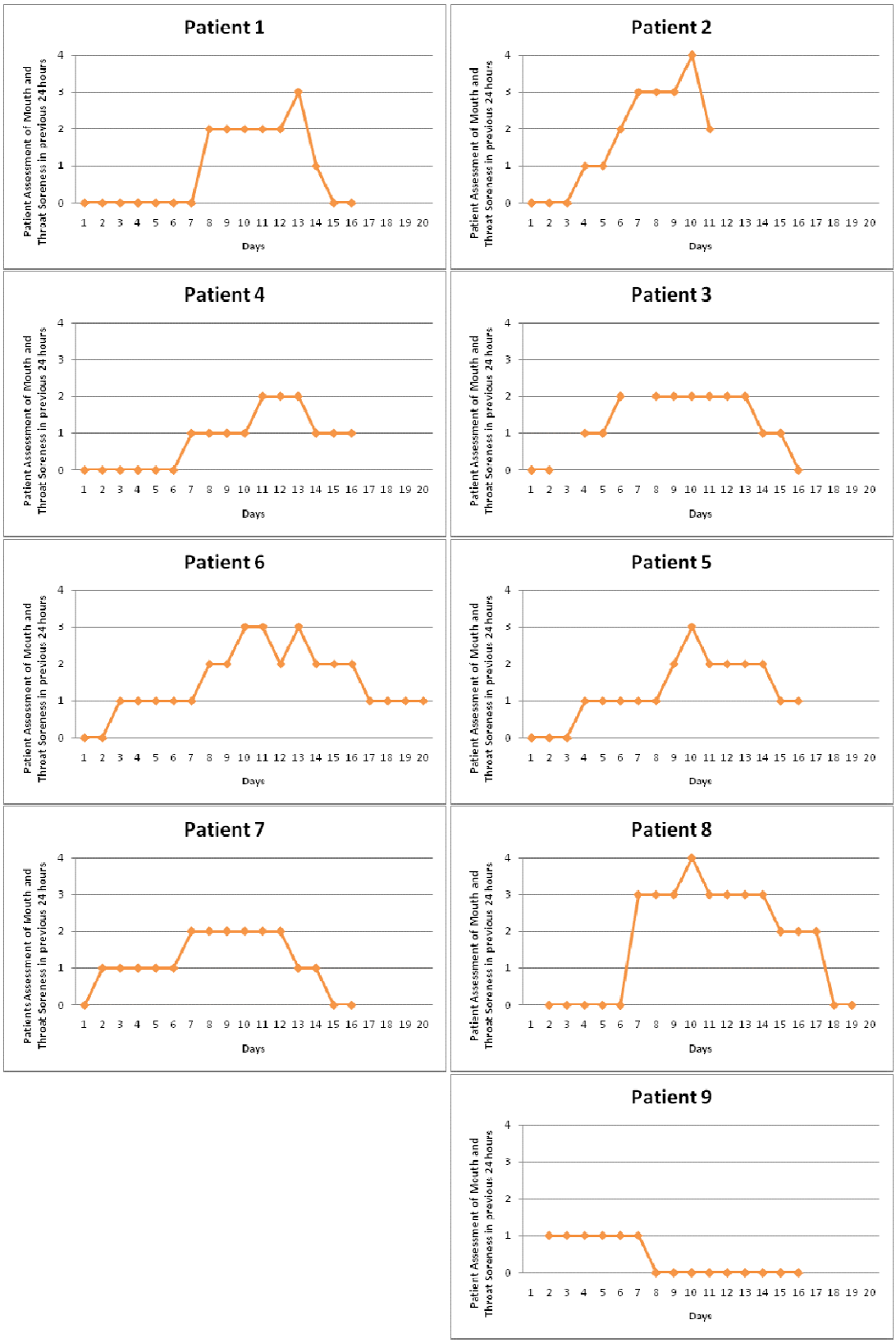


Figure 38: Patient Assessment of Mouth and Throat Soreness Plotted Against Time[36]

[36] A score of zero denoted no soreness, a score of four denoted extreme soreness

Figure 38 shows the patients' assessment of mouth and throat soreness experienced during the study. All patients experienced some degree of mouth and throat pain. Patient 9 reported a sore throat at baseline and gave it a score of one. No other patients reported mouth or throat pain at baseline. Patient 7 took the shortest time to report pain, indicating a score of one at the 2nd visit (day 0). Two patients (Patients 1 and 8) took the longest time to report pain, both experiencing pain for the first time at time point seven (day+5). Two patients reported the highest possible amount of pain on the subscale (a grade of four): Patient 2 reported a grade of four at visit 10, which coincided with a DIM score of 39 and a WHO score of three (Figure 36); Patient 8 reported grade four on visit 11 (day+9), which coincided with a DIM score of 37 and a WHO score of three (Figure 36).

8.4.5.3 Mouth and throat soreness limiting activities

Placebo Intervention

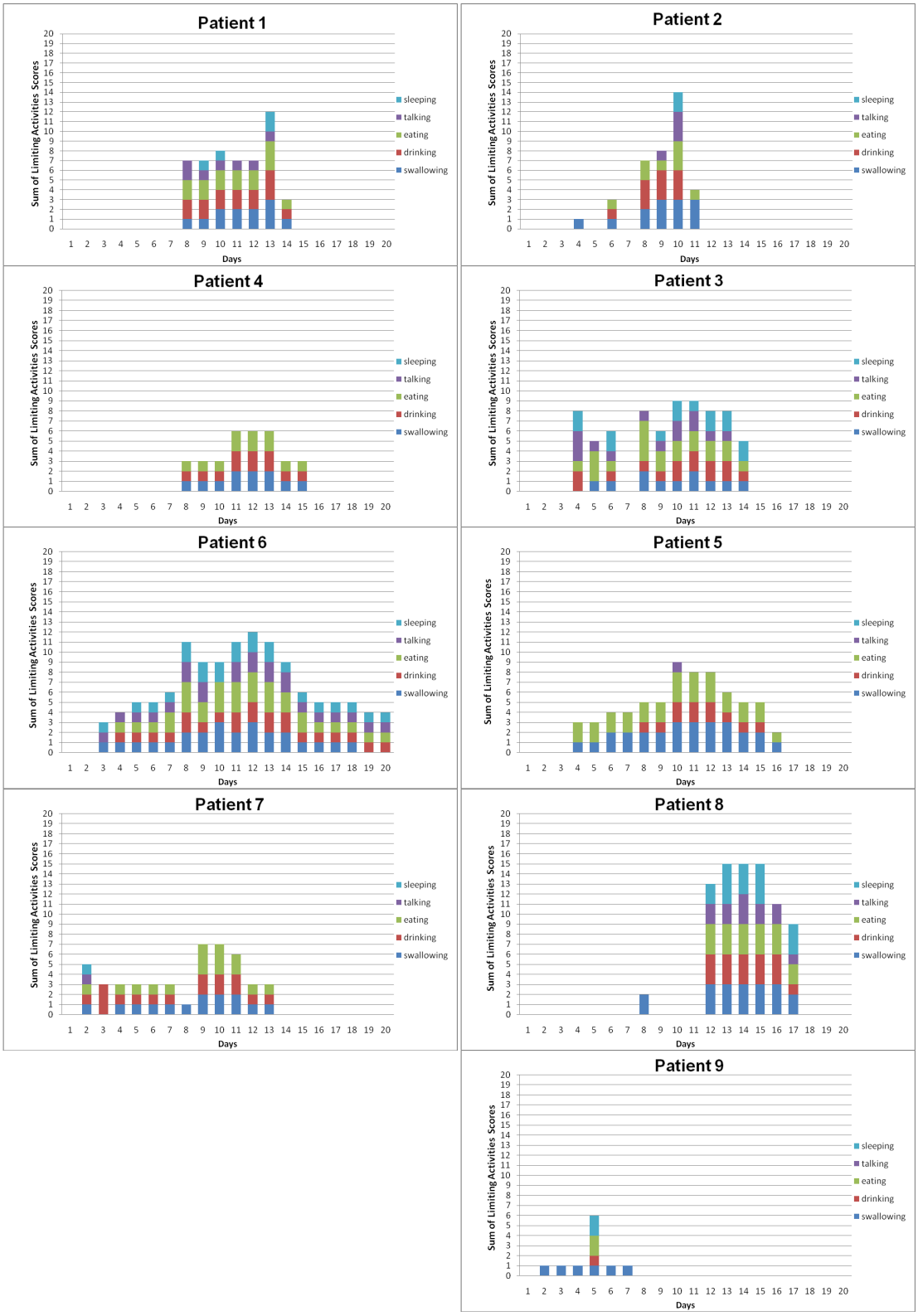


Figure 39: Limiting Activities Scores Due to Mouth and Throat Soreness Plotted Against Time[37]

[37] All categories graded from 0 (no limitation) to 4 (unable to do)

Figure 39 shows the limiting activities scores recorded by the patients. Patients were asked to score how any mouth and throat soreness was limiting their ability to sleep, talk, eat, drink and swallow on a five point scale, with zero as ‘no limitation’ and five as ‘unable to do’. Patient 6 (placebo) reported the greatest number of activities limited by mouth and throat soreness. Patient 8 (intervention) reported the highest scores for this limitation. Interestingly, in spite of not developing ulcerative mucositis, Patient 7 (placebo) experienced ‘a lot’ of limitation in eating at visits nine, ten and 11, suggesting that it may not just be the presence of ulcers that limits a patient’s ability to eat, and the severe erythema may be just as prohibitive to consumption of solids.

8.4.5.4 Overall Mouth and Throat Pain over previous 24 hours

Placebo | Intervention

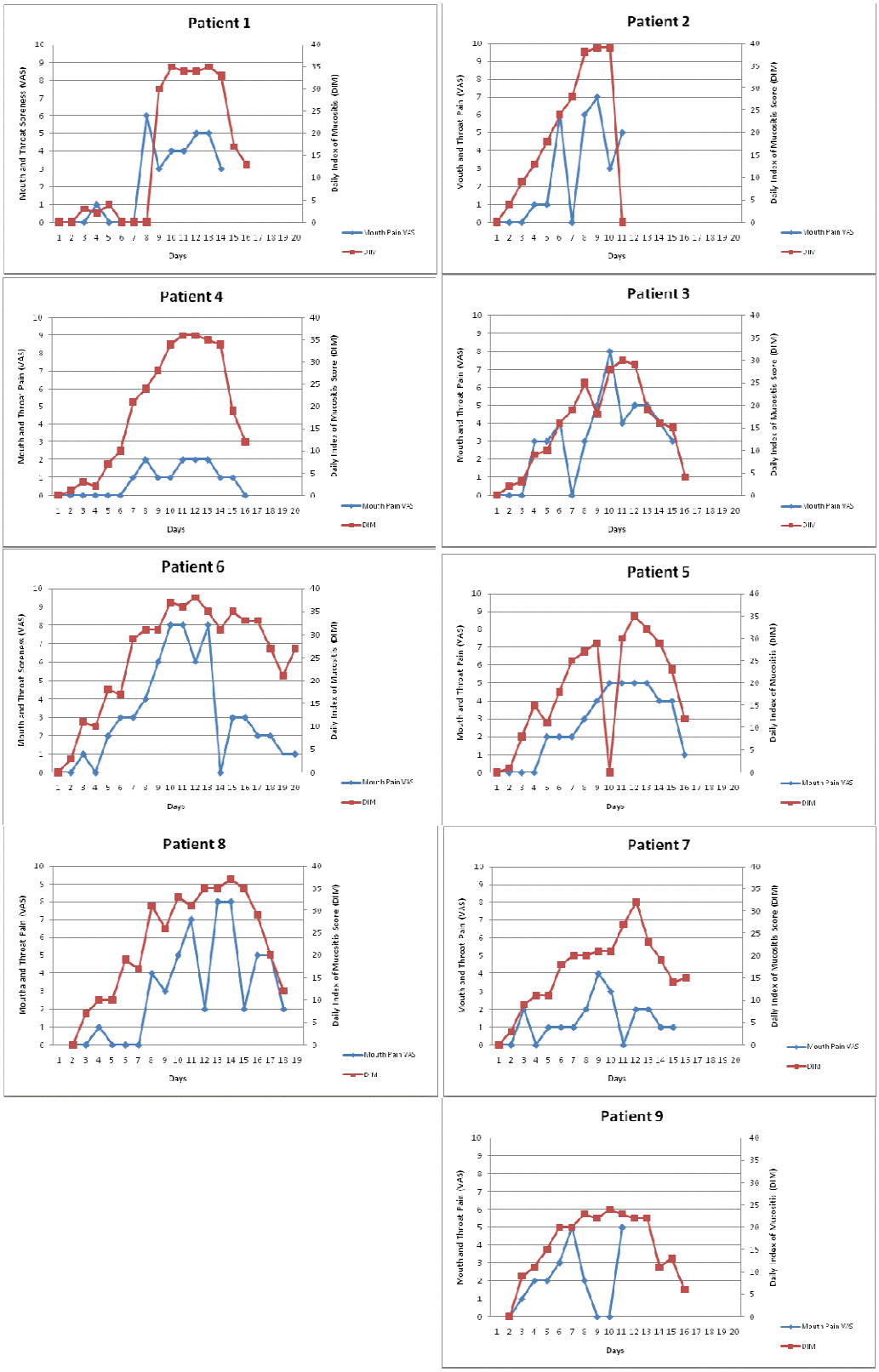


Figure 40: Overall Mouth and Throat Pain (VAS) Plotted Against Daily Index of Mucositis Scores[38]

[38] Mouth and throat pain graded from 0 (no soreness) to 10 (worst possible), DIM assessed from 0 (none) to 40 (worst possible grade)

Figure 40 shows the overall mouth and throat pain, recorded on a VAS, plotted against the DIM scores for each patient. This figure suggests some correlation between patient reports of pain and the DIM tool, particularly for Patient 3. With the exception of Patient 1, all patients started reporting pain a few days after a rise in VAS scores. The highest pain scores reported by the patients was a grade of eight. This score was reported by three patients (Patient 3: intervention, Patient 6: placebo, Patient 8: placebo), and in each case was associated with a peak in DIM score.

8.4.6 Nutritional scores

Patients were assessed using the Patient Generated Subjective Global Assessment Tool (PG SGA) once a week during supplementation. The first section of this tool, which is completed by the patient, asked about weight loss. A score of between zero and four (10% weight loss or greater) was calculated based on the amount of weight a patient had lost in the previous month. If the patient had lost further weight in the last two weeks an additional one point was added. The maximum score for this section is five.

The second section asked patients about their food intake. Patients are first asked to rate their food intake during the past month, with reports of eating less than normal given a score of one. The next section asked patients about quantities giving the following options: “less than a normal amount (score of one), “little solid food” (score of two), “only liquids” or “only nutritional supplements” (both score three), “very little of anything” (score of four). The final option is “only tube feedings” (score of zero). The maximum score for this section was five.

The third section asked patients to report any symptoms they have experienced during the previous two weeks. The presence of nausea, constipation, taste changes, a dry mouth, “smells bother me”, or “other” were each given a score of one. Reports of mouth sores or problems swallowing were each given a score of two. The existence of diarrhoea, pain, vomiting or a lack of appetite were each given a score of three. Therefore this section was scored out of a possible 23.

The fourth section asked about activities and function. Patients were given the following options: “normal” (score of zero), “not my normal self, but able to get up and about

with fairly normal activities" (score of one), "not feeling up to most things, but in bed or chair less than half a day" (score of two), able to do little activity and spend most of the day in chair or bed" (score of three), "pretty much bedridden, rarely out of bed" (score of three). The maximum score for this section was three.

Section five provides a score for the patient's condition. Each criteria: cancer, AIDS, pulmonary/cardiac cachexia, presence of an open wound/decubitus or fistula, presence of trauma, or age greater than 65 years old was given a score of one. The maximum score for this section was six. Metabolic stress was assessed in section six. Fever presence and duration and use of steroids were each graded from zero to three, giving a maximum score of nine in this section.

The final section of the instrument was a physical examination. Fat stores (three sites: orbital fat pads, triceps skin folds and the fat overlying the lower ribs) and muscles (seven sites: temples, clavicles, shoulders, interosseous muscles, scapula, thigh and calf) were graded from zero (none) to three (severe) for the amount of deficit identified through visual examination and gentle palpation of the sites. Fluid status (three sites) was also graded from three for presence of excess fluid. An overall score for each section was then calculated (mean value). The maximum score for this section was three. A total score for this instrument was then calculated by combining the scores for each section. The maximum possible score using this instrument was 54; however, it is extremely unlikely that a patient would score this anywhere near as high. Higher total scores using this instrument indicate that a patient was malnourished, while low scores indicate that a patient was well-nourished.

This instrument was chosen because it was recommended by the American Dietetic Association (ADD) as the standard for nutritional assessment in oncology patients. The researcher was concerned about the reproducibility of the assessments of fat stores, and muscle and fluid status prior to starting the trial. However, the PG-SGA training video gave good examples of mild, moderate and severe deficits in fat and muscle, which the researcher used to make sure she was continuing to be consistent in her assessments and that the results for this category were therefore reproducible between patients, and for the same patient over time.

No patient showed more than a mild deficit during the physical examination. This was most probably due to the relatively short time-scale that patients were assessed using the instrument. It could therefore be argued that while the decision to use the PG-SGA instrument in general, and the physical examination component in particular, in the feasibility study was valid, it might be better employed in studies of a longer duration.

Placebo **Intervention**

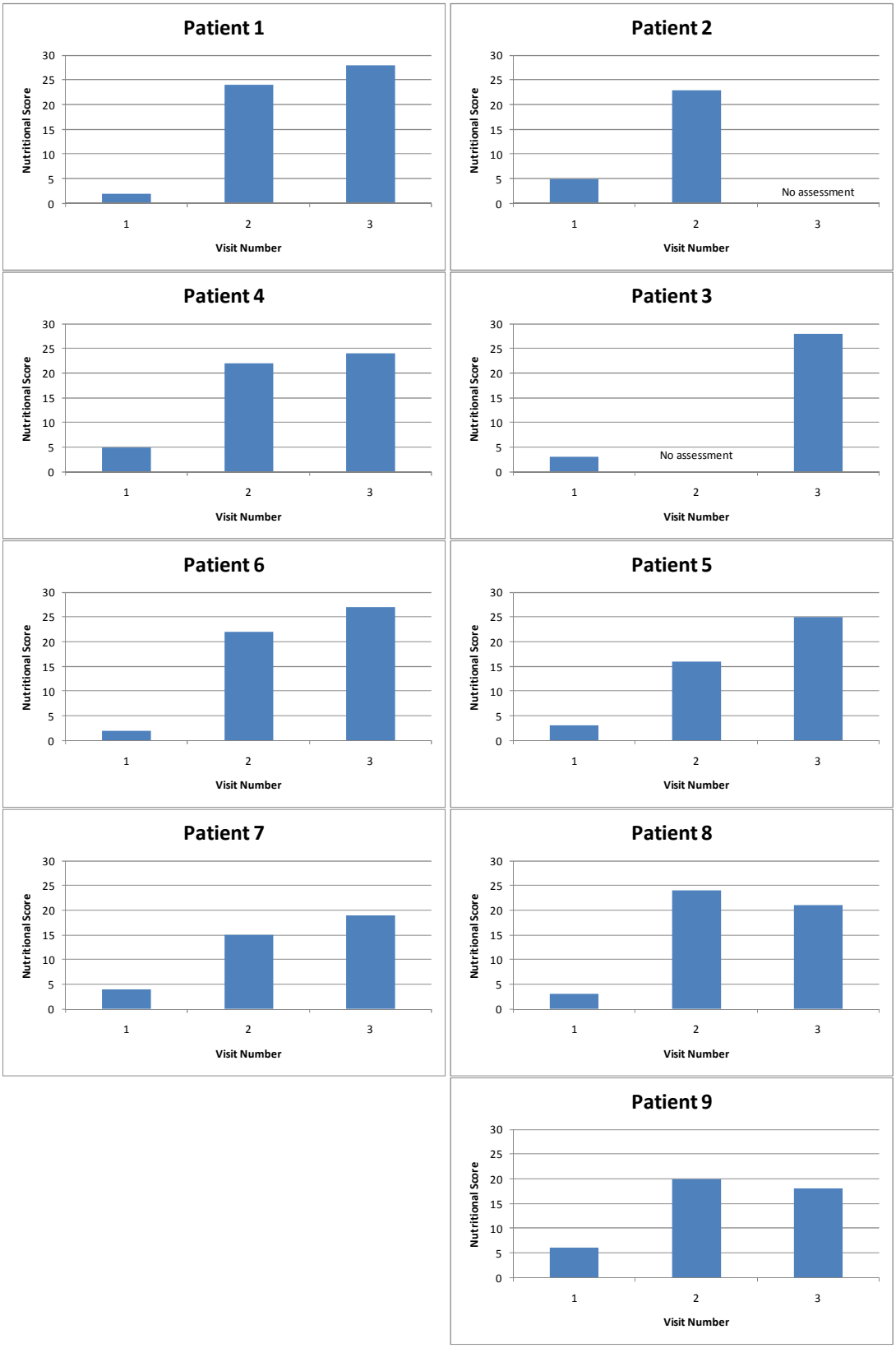


Figure 41: Total Subjective Global Assessment Scores [39]

[39] Low scores indicates that the patient is well-nourished, higher scores indicate malnutrition

Figure 41 shows the total nutritional assessment scores for each patient by assessment. Two patients missed an assessment: Patient 2 (intervention) was in the CCU when the 3rd assessment was due and Patient 3 (intervention) was suffering with nausea, vomiting and diarrhoea when the 2nd assessment should have been completed. Nutritional scores decreased for only two patients between visits two and three (Patient 8 and 9, both intervention). The highest score achieved was 28 out of a possible 44, this was recorded in two patients (Patient 1: placebo, patient 2: intervention). The lowest score achieved was by Patient 7 (placebo), this patient did not develop ulcerative mucositis and was able to eat during her transplant, which may have reduced her score.

8.4.6.1 Change in weight from baseline

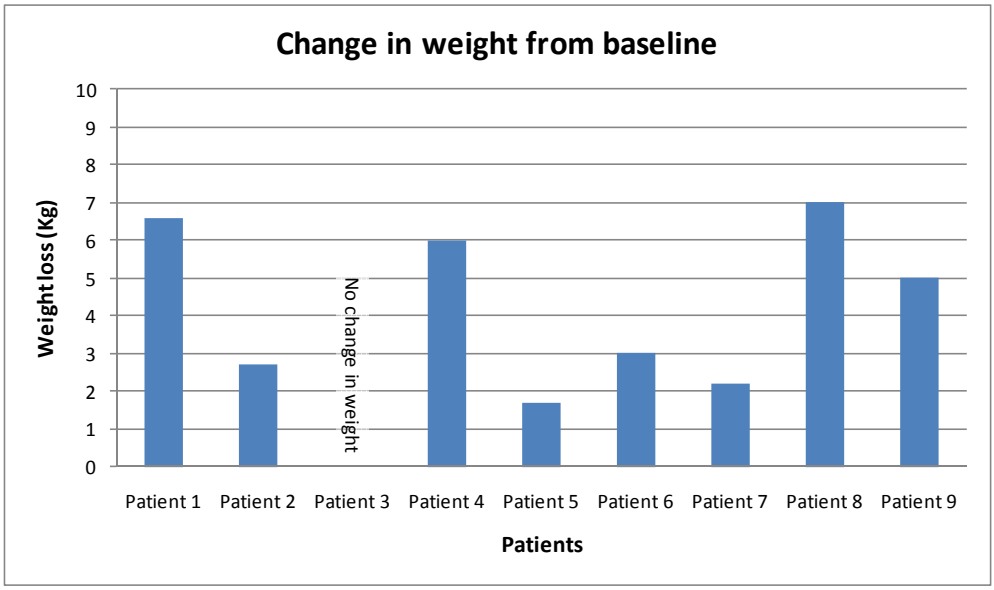


Figure 42: Change in weight from baseline[40]

Figure 42 shows the change in patient weight during the study. These data were collected at the same time as the patient was assessed using the subjective global assessment instrument. Patient 8 (intervention) experienced the greatest drop in weight, with a loss of seven kilograms (kg), corresponding to a 7% reduction in weight. Patient 3 (intervention) was the same weight at the first and third assessments; unfortunately weight data from assessment two were missing for this patient due to her inability to undergo nutritional assessment.

[40] Patient 3 experienced no change in weight

8.4.7 Adverse events and safety

Table 25: Adverse Events Experienced During the Study

Adverse event		Patient									Number of Patients in each arm experiencing event		
		1	2	3	4	5	6	7	8	9	Intervention	Placebo	Total
Blood / Bone Marrow													
White Cell Count *		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Haemoglobin *		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Platelet Count *		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Red Cell Count *		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Hematocrit *		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Mean Corpuscular Haemoglobin *		√	√				√		√	√	**3**	**2**	**5**
Mean Corpuscular Haemoglobin Concentration *		√	√	√	√	√		√	√	√	**5**	**3**	**8**
Neutrophils*		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Monocytes*		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Eosinophils*		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Basophils*		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Lymphocytes*		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Myelocytes ^							√				**0**	**1**	**1**
Presence of large Unstained Cells				√			√				**1**	**1**	**2**
Metabolic / Laboratory													
Adjusted Calcium*		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Alkaline Phosphatase^		√	√	√			√	√	√		**3**	**3**	**6**
Albumin	**Low**		√			√	√		√	√	**4**	**1**	**5**
	High			√							**1**	**0**	**1**
Total Bilirubin^			√								**1**	**0**	**1**
AST^			√						√	√	**3**	**0**	**3**
GGT^		√	√	√		√	√		√	√	**5**	**2**	**7**
Elevated LDH		√	√			√	√	√	√	√	**4**	**3**	**7**
Magnesium^			√	√				√			**2**	**1**	**4**
Phosphate	**Low**		√								**1**	**0**	**1**
	High	√		√	√	√	√	√	√	√	**4**	**4**	**8**
Potassium	**Low**		√				√	√	√		**2**	**2**	**4**
	High							√	√		**1**	**1**	**2**
Proteinuria				√		√		√	√		**3**	**1**	**4**
Serum Creatinine	**Low**		√								**1**	**0**	**1**
	High	√								√	**1**	**1**	**2**
Sodium	**Low**			√							**1**	**0**	**1**
	High		√			√	√				**2**	**1**	**3**
Urea		√	√	√	√	√	√	√	√		**4**	**4**	**8**
Gastrointestinal													
Constipation						√					**1**	**0**	**1**
Dehydration			√								**1**	**0**	**1**
Diarrhoea		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Nausea		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Vomiting		√	√	√	√	√	√	√	√	√	**5**	**4**	**9**
Xerostomia		√				√	√				**1**	**2**	**3**
Pulmonary/ Upper Respiratory													
Cough			√								**1**	**0**	**1**
Hiccups					√		√				**1**	**1**	**2**
Wheeze			√								**1**	**0**	**1**
Dermatology/ skin													
Alopecia		√		√	√	√	√	√	√	√	**4**	**4**	**8**
Dry Skin										√	**1**	**0**	**1**

Adverse event	Patient									Number of Patients in each arm experiencing event		
	1	2	3	4	5	6	7	8	9	Intervention	Placebo	Total
Rash									√	1	0	1
Injection site reaction								√		1	0	1
Constitutional Symptoms												
Fatigue				√	√	√	√	√	√	3	3	6
Fever			√				√		√	2	1	3
Rigors		√							√	2	0	2
Sweating		√								1	0	1
Weight Loss	√				√					1	1	2
Infection												
Febrile Neutropenia	√		√	√		√		√	√	3	3	6
Infection with grade 3 or 4 neutrophils	√	√		√		√				1	3	4
Cardiac Arrhythmia												
Sinus Tachycardia		√	√	√		√		√	√	4	2	6
Cardiac General												
Hypertension	√	√			√					2	1	3
Hypotension		√	√	√				√	√	4	1	5
Coagulation												
APTT^		√					√	√		2	1	3
Clauss Fibrogen*		√*								1	0	1
Derived Fibrogen^	√	√	√	√		√	√	√	√	4	4	8
Prothrombin Time^		√		√		√	√	√		2	3	5
Neurology												
Dizziness						√				0	1	1
Haemorrhage/ Bleeding												
GI Bleed						√				0	1	1
Nose			√							1	0	1
Pain												
Pain	√	√	√		√				√	4	1	5
Not classified												
Decrease in Globulin	√	√	√	√	√	√	√	√	√	5	4	9
CRP	√	√	√	√	√	√		√	√	5	3	8
Decrease in Total Protein	√	√	√	√	√	√	√	√	√	5	4	9

APTT= Activated partial thromboplastin time, AST=Aspartate aminotransferase, CRP=C-reactive protein, GGT=Gamma-glutamyl transpeptidase, GI=Gastrointestinal, LDH=Lactate dehydrogenase,

*decrease below normal limits as stated in the Common Terminology Criteria (CTC) (version 3) for adverse events

^ increase above normal limits as stated in the CTC v.3 for adverse events

Table 25 shows all adverse events recorded during supplementation and in the 30 days after the last dose. All patients experienced adverse events. Due to her chest infection and subsequent CCU admission, Patient 2 (intervention) experienced the greatest number of adverse events.

Two patients in the intervention group required an extra administration of G-CSF. Patient 3 developed an infection after supplementation had ceased which lead to a drop in her neutrophil count. G-CSF was administered and the patient subsequently discharged. This patient was seen in an outpatients' faculty close to home ten days after discharge and another drop in the neutrophil count (to $1.0x10^6$/kg) was reported.

However, she had started to regenerate her counts (to $1.70x10^6$/kg) when she was seen in outpatients (when follow-up ceased) five days later. Patient 5 also required another administration of G-CSF. This patient was discharged home with a neutrophil count of $1.40x10^6$/kg, which had dropped to $0.80x10^6$/kg when seen in clinic. This patient had lost 3.6kg in the ten days since discharge and admitted he "wasn't really eating anything". When followed up in clinic ten days later, this patient had a neutrophil count of $1.30x10^6$/kg. Both patients eventually developed neutrophil counts within the normal range ($2.00\text{-}7.50x10^6$/kg).

Three patients in the Intervention group had elevated levels of aspartate aminotransferase (AST), an enzyme used to monitor liver damage. However, two of these patients (Patient 2 and Patient 3) also had elevated levels at baseline. Patient 8 experienced an elevation of AST at day+2, three days after receiving chemotherapy and starting the trial, and at day+3. AST levels then returned to the normal range before becoming elevated again at day+16 (14 days after the cease of supplementation) and day+17, and at day+33 and day +46. This patient also had elevated levels of Gamma-glutamyl transferase (GGT), and when asked by a doctor, denied he had been drinking since discharge stating that he had previously been informed that his liver was very sensitive to paracetamol, which he had received almost daily during transplantation.

8.4.8 Conclusion of section two

The second section of this chapter has detailed the results of the feasibility study. As this trial recruited nine patients, the previously planned methods of analysis detailed in the study protocol could not be used. Therefore patterns of mucositis, pain and nutritional support indicators were discussed. This feasibility trial identified a difference between the data produced by the oral assessment instruments. The suitability of these assessment instruments, together with the suitability of the other methods of assessment will be addressed in the discussion. Furthermore, the discussion will consider the lessons learnt in the planning, conducting and analysis of the feasibility study. It is hoped that the lessons learnt through this feasibility trial will be utilised in the design of effective studies of interventions for the prevention of OM in the future.

Chapter 9 Discussion

This chapter will bring together the various elements of the previous chapters; it will consider the literature on the prevention of mucositis in terms of its risk of bias and practical issues arising during the conduct of published RCTs. It will discuss the assessment of mucositis within clinical trials and the choice of appropriate measurements tools. It will outline how these factors were used to inform the development of a feasibility study and how future trials should be conducted in light of the findings presented.

It has been well established that mucositis is a painful and distressing side effect of cancer treatment for patients (Borbasi et al., 2002, Cheng, 2009), which has a substantial clinical and economic impact, manifested through an increased need for opiates and other supportive therapies, longer duration of hospitalisation (Vera-Llonch et al., 2007a) an increased risk of infection (Ruescher et al., 1998), and in severe cases, dose modification or treatment breaks to allow the patient to recover (Peterson and Cariello, 2004). The prevention of mucositis in patients treated for cancer is an area that receives much attention from research groups, with 130 published trials currently included in the Cochrane review on this topic. Thirty three trials investigating a variety of interventions for the prevention of mucositis are also listed as ongoing on Current Controlled Trials. Given the importance of this topic and the resources that go into conducting these trials, it is imperative that the trials are conducted to the highest possible standard if they are to inform clinical practice.

Gaps between research findings and interventions used in clinical practice have been identified in the feasibility study and in the literature, particularly in the use of chlorhexidine for mucositis prevention (Barker et al., 2005, Glenny et al., 2004). Such gaps may be a consequence of Clinicians finding it difficult to keep on top of the huge volume of literature in this field. The use of systematic reviews and guidelines are methods of closing such gaps. Systematic reviews are often used as building blocks for the development of guidelines and for the drawing up of recommendations. However, for these reviews to be of most use, they need to be based on the results of high quality trials. An integral part of Cochrane reviews is the assessment of trial quality. The recently introduced risk of bias instrument assesses the internal validity of trials

(Hartling et al., 2009) by assessing the risk of potential biases across eight domains: sequence generation, allocation concealment, blinding (carers, patients and outcome assessors), incomplete data reporting, selective outcome reporting and other (Higgins and Altman, 2009).

The application of the new ROB tool to the prevention of mucositis trials have shown 83 trials to be at unclear ROB and 38 studies to be at high ROB. It is disappointing that out of 130 trials included in the Cochrane review and 43 interventions studied, only nine interventions have been shown to be potentially beneficial, and of these only one intervention, antibiotic pastille or paste, is supported by trials of low risk of bias, and even then, this result is only for the prevention of severe mucositis, as the other domains of interest were excluded from the analysis. However, one drawback when using the ROB instrument is that only what is reported in the paper can be assessed, and therefore studies which were well conducted but poorly reported may be misrepresented (Nuesch et al., 2009).

By taking a closer look at the methods used within the previously published trials, both in terms of ROB and practical issues, and by drawing on experience from the feasibility study, we can gain a realistic picture of how future trials can be conducted in a way that ensures the results are at low risk of bias.

9.1 Regulatory requirements/ pharmacy approval

One of the first stages in the undertaking of a clinical trial is ensuring that all regulatory requirements are met, including ethical, regulatory and hospital trust approvals. The time taken for the start-up of the feasibility trial, measured from the researcher's first contact with the Hospital research and development department to the first patient starting the trial was 14 months: a number of delays were experienced in setting up the study. Before the MHRA application could be submitted an Investigational Medicinal Product Dossier (IMPD) had to be written by Preston Pharmaceuticals. Completion of this dossier required additional information to be requested from the manufacturer (Capsugel), through the supplier (Healthplus). This was especially difficult due to a lack of understanding on the part of Healthplus with regard to the Ethics and MHRA

application process. It is possible that many of these problems could have been avoided had another supplier been selected to provide the intervention and placebo products. Further delays were experienced in waiting for the products to be packaged and dispatched by Preston Pharmaceuticals. The need for QP release of trial supplies has been identified in the literature as a barrier to the conducting trials, as this increases trial costs and delays (Duley et al., 2008). Recruitment in this feasibility study ceased when the sell-by date for the intervention was reached on 30th June 2009. Extension of the recruitment period would have required a reapplication to the MHRA with a new IMPD, which given the delays already experienced and the length left in the Researchers doctorate program, was not considered to be feasible. Future studies should keep such issues in mind when going through the regulatory approvals process.

The greatest delays experienced during this study were while waiting for NHS Trust approval. However, since completing this trial, the researcher has heard of anecdotal accounts of Trust approval for other trials conducted at the same hospital taking in excess of a year to be granted or declined, which suggests that the six months wait for this trial may have been comparatively rapid. Had the researcher and her supervisors not taken a chance in purchasing the intervention and placebo capsules and organising for them to be packaged prior to Trust approval being granted then it is likely that even greater delays would have been experienced in starting this trial. In addition, it is likely that the delays experienced during the set-up of this trial would have been considerably longer had it been a multi-site study. Bearing in mind that the trial in question was a non-commercial study, it is worth considering that this timeframe may have been shorter had the trial been funded by industry. Nevertheless, the 14 month timeframe identified in this trial may actually be relatively short compared to some studies, as timeframes as long as two years have been identified in the literature (Dilts et al., 2006).

While the application process for Ethics and the MHRA have been combined since this trial gained approval, there is no reason to suppose that the approvals process has become more rapid since 2008, especially since the Trust approval process has remained the same. The Trust may therefore need to strike a better balance between ensuring rigorous research governance and making sure that the approvals process does not take so long that it discourages research. Approvals processes in excess of 14

months would have a significant impact on the feasibility of conducting future doctoral projects, and may force the abandonment of a clinical trial as a suitable thesis project. Macdonald and colleagues (2006), conducted a review of 114 trials which were funded through two united Kingdom funding bodies, and reported that 41% experienced delays in recruitment. The majority of the reported delays concerned staffing (22 trials), however delays in receiving necessary approvals, in the supply of intervention or placebo products and delays due to clinical arrangements are also reported (McDonald, 2006), all of which were experienced by the feasibility study. Therefore taking into account the delays experienced during this study, the majority of which were due to the regulatory process, future studies in this area should set aside at least a year for all approvals to be gained.

9.2 Clinician interest

Several of the problems arising during the feasibility trial may have been avoided by ensuring clinical staff had input into the protocol design. This may have ensured that concerns raised about the trial could have been ironed out prior to the study commencing. It might also have given staff a sense of ownership of the trial and improved collaboration. However, given the dynamics of staff working on the unit at the time of the trial it is unlikely that all issues would have been resolved. For example, the recruitment of allogeneic patients may still not have been possible.

Barriers to, and motivational factors for, Clinician participation in clinical trials, have been extensively reviewed (Fallowfield et al., 1997, Keinonen et al., 2003, Raftery et al., 2009, Rendell et al., 2007), however many of the issues identified are not applicable to small non-commercial studies, such as this feasibility study, as they focus on the use of Clinicians to recruit patients into either large multi-site commercially funded studies, or barriers to Clinicians conducting their own research. However, an interest in the research question has been suggested as a factor motivating Clinicians to participate in trials (Keinonen et al., 2003, Raftery et al., 2009). Taking into account the lack of a ward policy for the prevention of mucositis and the *ad-hoc* nature of treatment when oral conditions did develop, it seems reasonable to conclude that mucositis may not have been a research priority for the Clinicians on the ward, and that this was therefore a barrier to their participation in the feasibility study.

9.3 Identifying eligible patients

Eligible patients were identified through the researcher's attendance at the weekly transplantation meeting and subsequently through the discussion of any potential patient with their treating Clinician. This method worked well, but tended to fall down during the holidays, or in one instance, when all four consultants were attending a conference. During such times the transplantation meetings were cancelled and a list of patients circulated by email. This was initially problematic for the researcher, as it was 'hit and miss' whether she would receive such emails. Occasionally patients would also move up and down the transplant list depending on the availability of a bed, or the need for emergency admissions, which resulted in some patients being missed by the researcher during their outpatients' appointment. However, the development of a good working relationship between the researchers and the transplantation co-ordinators as the trial went on, helped the researcher keep track of changes to the list and made this process easier. Eligible patients were approached during outpatients' appointments in the presence of the treating Clinician. Patients who were missed in the outpatients' clinic were approached on either the day ward or after admission to the unit in the presence of a member of the nursing staff. The method of identifying eligible patients employed in this trial proved to be feasible and could be employed in a future trial.

9.4 Feasibility of patient recruitment

The feasibility study aimed to recruit six patients for the pilot and 60 patients for the main feasibility study, resulting in an overall sample of 66 patients. This sample size was decided after discussion with a statistician, who helped the researcher interpret the literature concerning power calculations and advised that in order to estimate a parameter, such as a mean or median value, 30 patients or greater are required (Lancaster et al., 2004). In this case, an additional 30 patients would be required to estimate a standard deviation, resulting in a sample of 60 patients for the main feasibility study. An additional six patients were to be recruited for the pilot to check that patients were able to follow the protocol and that the data collection sheets were adequate. This study was not designed to be powered to detect differences between the groups for the prevention of mucositis or any other parameter. However, it was thought

that the results of this study would be used to inform a sample size calculation of a future study.

Unfortunately, the problems experienced in recruiting patients to the project together with the low number of patients taking part in the study preclude sample size calculations from being conducted using data from the feasibility study. Eighty-four patients underwent transplantation in 2007 in the unit, and as the unit had been expanded to accommodate more patients it was conceivable at the time of writing the protocol that the pre-specified aim of recruiting 66 patients for this study was achievable. However, the length of time taken to achieve regulatory and Trust approval, together with the problems recruiting allogeneic patients into the study, resulted in a greatly reduced recruitment pool of patients being available to the researcher.

Eighteen patients were approached to take part in the feasibility study and nine patients were recruited, with the remaining nine patients declining to take part in the study. Patient recruitment into RCTs has been reported to be a significant problem (Prescott et al., 1999). Jenkins and Fallowfield (2000), attempted to identify patient's reasons for accepting or declining to participate in clinical trials in a study conducted in patients with a mix of cancer types After discussion with a Clinician about clinical trials for which they were eligible, patients were asked to complete a questionnaire detailing their satisfaction with the consultation and their reasons for accepting or declining to participate in the proposed trial. Of the 204 patients who completed questionnaires, 147 (72.1%) gave consent to take part in the trial proposed by their Clinician, with altruism: a belief that their participation would benefit future patients with the same condition, being the most frequently cited reason for participation. Notably, of those declining to participate, 32 patients (62.7%) stated that the idea of randomisation worried them, with ten of these patients stating that this constituted the most important factor in their decision in declining to take-part (Jenkins and Fallowfield, 2000). Such an aversion to randomisation has also been reported by Llewellyn-Thomas and colleagues (1991), who reported that 58% of colorectal patients approached to participate in a study declined to participate, with 63% of patients who refused citing an aversion to randomization as their main reason (Llewellyn-Thomas et al., 1991).

In a sub-set analysis of the Jenkins and colleagues (2000) study, the patient acceptance rates of trials which included a no treatment arm were compared to those of trials with an active treatment in all arms of the study. In this analysis, patients were found to significantly favour the active treatment arms option, with 80.6% of patients responding favourably to the active treatment studies compared to only 60.5% of patients in the no treatment studies (P=0.003). This sub-set analysis also showed that placebo arms were associated with high levels of acceptance, with 22 of the 24 patients offered a trial including a placebo arm deciding to enter the trial. However, the authors point out that this finding might be spurious as 19 of these patients were recruited by the same member of staff (Jenkins and Fallowfield, 2000), and it is therefore possible that this affected the result. It was clear to the researcher that the random element of this study was not favoured by some of the eligible patients. Several patients verbally stated a preference for the intervention of interest; while other patients made facial expressions of displeasure when they were informed that they had an equal chance of being allocated to the placebo group. The need for patient blinding was also met with a similar reaction by several patients.

Patients have reported that they find the idea of randomisation confusing (Featherstone and Donovan, 1998), and that they would rather leave treatment decisions to the Clinicians rather than to chance (Gotay, 1991). Research into the descriptors of randomization employed in patient information sheets has also found that patients favour some descriptors of randomisation over others (Jenkins et al., 2005). In a study conducted by Jenkins and colleagues (2005), seven descriptors of randomisation were chosen from patient information sheets, and 600 patients were asked to indicate which statements they disliked and which ones they preferred. The most preferred description of randomisation in this study was one taken from the Cancerbackup website, which has since merged with Macmillan cancer research. This definition stated:

> "(*randomisation*) ... means that a computer randomly puts patients into the treatment groups in the trial. Each group has a similar mix of patients of different ages, sex and state of health" (Macmillan, 2010b, randomisation 1st paragraph).

Interestingly, this was the only one of two definitions that made no reference randomisation being down to chance (Jenkins et al., 2005). The most disliked descriptor was taken from the National Cancer Institute (NCI) website, and stated:

> "(*randomisation*)...is a process that assigns participants by chance, rather than by choice, to either the investigational group or the control group" (National Cancer Institute, 2010, 1st paragraph).

Participants reported that this definition was too complicated (Jenkins et al., 2005). The descriptor of randomisation used in the feasibility study was taken from the NRES guidance documents on consent forms and patient information sheets (National Research Ethics Service, 2009), and is dissimilar to those assessed in the Jenkins and colleagues study, stating:

> "Sometimes we don't know which way of treating patients is best. To find out, we need to compare different treatments. We put patients into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly)" (National Research Ethics Service, 2009, 15)**.**

Although it appears to offer an easy-to-understand definition of randomisation, it is unclear if such a descriptor has been investigated using similar methods to those of Jenkins and others (Jenkins et al., 2005), to gauge patient opinion. Whilst patient preference for randomisation descriptors is an interesting topic, it is currently unclear if the descriptor of randomisation used in the patient information sheet affects actual recruitment rates. However, it may be wise to avoid overly complex descriptors of randomisation, such as shown on the NCI website, in future studies.

In addition to concerns about randomisation, other barriers to patient participation include: a concern about treatment toxicity, a fear of the potential for loss of control, a preference for a particular treatment and the inconvenience of being involved in the trial and a personal preference for a particular treatment (Ellis, 2000). Certain groups of patients may be more receptive to the idea of a clinical trial than others. Patients who are naturally altruistic may be more likely to consent to research (Bevan et al., 1993, Jenkins and Fallowfield, 2000). In addition, various demographic factors may also be

important: patients who are male, older, less educated and from lower socioeconomic backgrounds have been reported to be more likely to take part in clinical trials (Ellis, 2000, Gotay, 1991, Prescott et al., 1999), while ethnic minorities tend to be underrepresented in clinical trials (Roberson, 1994).

Recruitment problems were a persistent theme in the studies assessed for ROB in chapter four. Six studies assessed for ROB described randomisation problems; however, four of these did not detail the specific nature of the problems. One study experienced a high rate of refusal (McAleese et al., 2006). Gandemer and colleagues (2007), in their chewing gum study, stated that nurses found it difficult to devote time to patient assessment. This lack of support staff availability is a common problem and has been reported as a barrier to the recruitment of patients. Clearly, recruitment will be significantly hampered if support staff, usually research nurses, have a large number of trials for which they need to recruit patients and collect data. The need for research staff to have time dedicated exclusively to a trial has been highlighted in the literature (Prescott et al., 1999), however, this still appears to be an on-going problem. Large multi-site, industry-sponsored trials frequently contribute financially towards research nurse time, or provide a payment to the hospital for every patient recruited. However, this may not be an option in many small, non-commercial studies, resulting in such studies being overlooked. The perceived importance of the research project to a researcher may also influence the amount of time and effort that gets put into recruitment, as researchers may be motivated to expend more effort on projects they perceive as more novel or important (Prescott et al., 1999).

Slow patient accrual is therefore an established problem in clinical trials (Cox and McGarry, 2003), and one which appears to be especially challenging in trials conducted in patients with cancer (Jenkins and Fallowfield, 2000). The use of multi-site studies obviously leads to higher rates of recruitment, however, conducting studies on more than one site may not be a possibility due to financial or staffing constraints (Gul and Ali, 2010). Planning for longer periods of patient recruitment may help alleviate recruitment problems. In addition, the use of monthly or weekly recruitment targets may be beneficial, as they act as a constant reminder that staff need to focus on recruitment. However, such targets need to be frequently reviewed to allow for the recruitment

strategies to be changed and new strategies adopted (Gul and Ali, 2010). In their multi-site study which compared diet and exercise, or medication, to placebo for the prevention, or delay in the onset, of type II diabetes, Rubin and colleagues (2002), describe the use of recruitment liaisons, who were in contact, on a monthly basis, with each site and helped to identify and resolve recruitment issues (Rubin et al., 2002). In those sites requiring more assistance, a stepped process of increasing contact was used, which included conference calls with key members of staff to address issues. If a site continued to experience problems after this period of intervention, they were visited by a member of recruitment liaison staff for a period of intensive help (Rubin et al., 2002). However, despite the best efforts of staff, four sites in this study did not reach their recruitment goals, indicating just how difficult recruitment can be.

During the feasibility study, it was stipulated by the Ethics Committee that the first approach of any patient meeting the inclusion criteria was to be made by a member of the medical staff. However, it is possible that this approach may have had an impact on patient recruitment, especially if the member of staff was not properly educated about the aim and methodology of the trial, as this could misrepresent the study to the patient, which could impact their decision to consent to take part in the trial (Gul and Ali, 2010). Prior to the start of recruitment for the feasibility study, the researcher presented the project to unit staff in a lunchtime seminar series. However, less than 50% of the unit staff were present at this meeting, which meant that the researcher had to introduce, or reintroduce, the study to staff on the unit before asking them to approach the patient. It is possible; therefore, that some of the staff who made the first approach to the patient did not have a full understanding of the trial. Unfortunately, as such introductions were often made without the researcher being present, it is not possible to know what was said, meaning that no connections can be drawn between whether or not the staff member had been educated about the study, and whether the patient consented to take part in the study. If future studies are asked to use a member of the medical team to approach patients first, then it seems sensible to implement an extensive education programme on the units from which patients will be recruited. Such a programme could include an introduction talk to RCTs in general, and then to the trial (McDonald, 2006). This talk should be repeated at least once, to ensure staff are able to attend. In addition, the trial should be advertised on the ward, with copies of the patient information sheet,

or an introduction to the study sheet specifically written for staff, made available nursing and doctors' offices.

Major recruitment issues such as patient confusion with, or mistrust of, random allocation is only going to be resolved by more effective education of potential participants. It is possible that the provision of patient information booklets about clinical trials, together with the patient information sheet, may alleviate patient confusion about clinical trials. Such publications are produced by a number of different cancer charities and are widely available. Such publications may also be trusted by the patient as they are produced by a source external to the hospital or research group. Another method which has been suggested to boost recruitment of patients into clinical trials is the use of remuneration for travel expenses or monetary compensation for the patient's time. However, the use of such compensation is controversial, especially if the value of compensation is high, as it could be coercive (Gul and Ali, 2010). In addition, as the patients in the feasibility study were inpatients, and therefore did not have travel expenses, it is difficult to see how the use of compensation would have worked in the present study. The nature of the recruitment problems experienced during this trial support the use of feasibility studies to explore such issues before opening full studies of future interventions.

In the feasibility study, nine patients were recruited over the 35 weeks in which the study was conducted, giving a patient per week calculation of 0.26 patients/week. This study aimed to recruit 66 patients. By extrapolating this recruitment rate it can be calculated that it would have taken an additional 219 weeks, or 3.84 years, to reach the previously specified number of patients. Seventy-nine of the 130 studies assessed for ROB contained enough information for the calculation of recruitment rate for these studies. These recruitment rates ranged from 0.153 patients a week in a study of glutamine in patients with solid tumours receiving chemotherapy (Alvarado et al., 2002) to 7.66 patients per week in a multi-site study of iseganan in patients with head and neck cancer (Trotti et al., 2004). The mean average rate of recruitment for all studies which provided enough information, was 1.13 patients per week, however, after the removal of multi-site studies, which could be reasonably expected to experience higher rates of recruitment, the mean average rate of recruitment fell to 0.79 patients per week

for the single site studies. In addition to patient refusal to participate, the recruitment rate for this trial was affected by other factors, such as a lack of access to patients, which limited the number of patients available for the researcher to recruit. It is likely that for future trials, the expected rate of recruitment would be much higher and similar to the average calculated for the single site studies assessed for ROB.

9.5 Feasibility of informed consent

After approaching patients to take part in the trial, the researcher returned at least 24 hours later to ask the patient whether they would like to participate. The shortest duration between initial approach and the patient being asked for a decision was 26 hours. This patient, who did not want to participate in the study, was approached to take part after he had already been admitted onto the ward. The longest duration between approach and patient decision was five weeks. This patient consented to take part in the study, and was the fifth patient to be randomized. Seven patients were admitted the day before starting chemotherapy. These patients were admitted from the day unit first thing in the morning, and then were sent to another area of the hospital for Hickman line placement. It was generally mid-afternoon before patients arrived on the transplant unit. After being allocated a room, patients were given a ward orientation and booked in by their nurse. They were also seen by a doctor who medically assessed them prior to initiation of treatment as per standard operating procedures. The researcher found it difficult to speak to the patient during this period due to the number of other people who also needed to access the patient; a problem which was compounded by the presence of the patient's family and friends. The researcher therefore spent a large amount of time waiting around on the ward for the patient to be free. If the patient chose to consent to take part in the study the researcher asked them to complete the consent forms and got a doctor to sign the prescription securing the pharmacy release of the products. The method of informed consent employed in the feasibility study was feasible. However, ethical clearance to recruit patients from the day unit first thing in the morning, before they received their Hickman line would be a useful addition to the informed consent procedures planned for future studies.

9.6 Feasibility of randomisation

Only 26 studies (19.8%) assessed for ROB were judged to have adequately described the randomisation process. Twelve of these studies employed computer generated sequence generation. This method of randomisation was also used in the feasibility study. The School of Nursing, Midwifery and Social Work Statistician used a computer program to create a randomisation schedule, which he then sent to Preston Pharmaceuticals. The intervention and placebo products were packaged by Preston Pharmaceuticals using this schedule, in sequentially numbered packages of identical appearance. Packaged trial products were then delivered by Preston Pharmaceuticals to the hospital pharmacy by courier and the researcher was provided with a list of numbers which was used to allocate each new patient the next number in sequence. Intervention and placebo products could not be dispatched out of sequence because the pharmacy were dispatching the products and were completing the trial paperwork, which prevented the products being released out of order. The method of randomisation employed in this study was feasible and could be employed in future studies.

9.7 Feasibility of allocation concealment

Seventeen studies (13%) of the trials assessed for ROB described adequate methods of allocation concealment. Seven (5%) of these studies employed pharmacy controlled randomisation, while two studies (1.5%) described the use of sequentially numbered drugs containers of identical appearance. Nuesch and colleagues (2009) conducted a review of 16 meta-analyses in a meta-epidemiologic study of trials of interventions for osteoarthritis, and used the ROB assessment instrument to compare the effect sizes of interventions assessed at low ROB to those assessed at high or unclear ROB for the allocation concealment and patient blinding domains. 46 trials (29%) were judged to be at low ROB of bias for allocation concealment in this review, with sequentially numbered drugs containers being the most frequently used method of allocation (26 studies), followed by central allocation (15 studies) (Nuesch et al., 2009). The authors report a trend towards smaller effect sizes in studies with adequate allocation concealment being less beneficial than those assessed as unclear or at high risk of bias (Nuesch et al., 2009). Similarly, trials with large effect sizes were significantly associated with a judgement of unclear or high risk of bias for allocation concealment (Nuesch et al., 2009). The authors conclude that adequate allocation concealment should be ensured in future trials (Nuesch et al., 2009).

The feasibility study employed both central randomisation and sequentially numbered drugs containers of identical appearance as methods of allocation concealment. Early during the study one of the consultant Clinicians asked that a copy of the randomisation schedule be placed in the study file, to ensure that this information could be accessed quickly in an emergency, such as a SUSAR. This was rejected by the researcher and her supervisors on the grounds that this study file was freely available on the ward and could be accessed by any member of staff, including the researcher. A compromise was reached by one of the researcher's supervisors emailing a copy of the schedule to the consultant. This was then stored on the consultant Clinician's computer. When asked by the researcher, the consultant stated that he had not looked at the schedule as he wanted to be able to make decisions regarding adverse events without prior knowledge of allocations, but also wanted to be able to reach this information, if he needed it, quickly. Clearly, in future trials a balance needs to be reached between ensuring adequate allocation concealment and making sure emergency unblinding procedures can be conducted. In order that the treatment allocation for an individual patient be known, but that allocation concealment is maintained for all current and future patients, individual allocations could be concealed through a series of sealed envelopes. The methods of allocation concealment employed during this study proved to be feasible for use in future trials. Careful consideration needs to be given to unblinding procedures in the event of a SUSAR.

9.8 Feasibility of pharmacy release

Allowing time for pharmacy release was an area of concern, as there was only a window of approximately two hours between the patient arriving on the ward and the pharmacy closing for the day. The development of a good working relationship with the unit pharmacist, who knew which patients were eligible for the project and when they were being admitted onto the ward, helped the researcher meet the pharmacy deadlines. This pharmacist would check with the researcher whether or not a patient had consented to take part in the study before he went up to the pharmacy to deliver prescriptions for the unit, and if a patient had consented to take part, the pharmacist would personally fill the prescription and place it in the evening pharmacy delivery box, so that the researcher

was reassured that the patient would receive the intervention or placebo that evening, after the researcher had gone home for the evening.

9.9 Feasibility of blinding

Blinding was assessed in three criteria for the studies included in the ROB analysis shown in chapter four, these were patient blinding, carer blinding and outcome assessor blinding. Nineteen studies described carer blinding adequately. Seventy-five studies were assessed to adequately describe patient blinding and 77 studies were deemed to describe suitable methods of outcome assessor blinding. The term 'double blind' was used extensively in the mucositis literature. However, this term lacks a standard definition, as in addition to patients and outcome assessors it can also be used to describe the blinding of outcome assessors and clinical staff or patients and clinical staff (Viera and Bangdiwala, 2007). Therefore a sub-set analysis was conducted for studies which explicitly stated that the outcome assessor was blind, and revealed that only 19 studies (14.5%) gave specific information that outcome assessors were blind, while all other studies in this category only described themselves as double blind. Blinding of patients was impossible for three interventions included in the Cochrane prevention review as there was no suitable control which would be used. These were: cryotherapy, dental stent and honey. The use of outcome assessor blinding in such trials is therefore of upmost importance. However, only one of these trials employed such blinding (Motallebnejad et al., 2008). Two of these studies were found to be beneficial for the prevention of mucositis at all three levels of interest in the Cochrane prevention review, however, the lack of outcome assessor blinding renders such results unreliable.

The feasibility study went through the Ethics and MHRA approvals process as a single blind trial because the researcher and her supervisors were unsure how feasible it would be to conduct a double blind study with only one researcher. However, pharmacy release of sequentially numbered identical packages, which had been packaged by a third party, ensured adequate allocation concealment, and as the researcher did not have access to the randomisation sequence, blinding was successfully maintained throughout the study. In addition, the researcher did not actually see the intervention or placebo capsules until after the study had been completed as the ward pharmacist performed the capsule counts, which were performed to check compliance. The researcher was

therefore unaware of the allocation sequence until after the blinded AUC analysis was conducted by the statistician and the codes were broken by one of the researcher's supervisors. Patient blinding was maintained by all patients being barrier nursed in isolation. Support staff on the unit were also blind to the treatment allocation, due to the use of pharmacy release. Conducting future trials with the lead researcher blind to the allocation concealment is therefore feasible, if care is taken in setting up the trial. There is no reason why future studies cannot be performed with adequate outcome assessor blinding. Specific information about which members of the research team were blind should be included in all future publications.

9.10 Feasibility of stratification

Stratification is a process whereby patients are grouped according to pre-specified criteria hypothesised to affect the outcome of interest. Each group is then separately randomised to receive a treatment. Stratification is important in studies which recruit fewer than 100 patients, due to the risk of imbalance (Kernan et al., 1999). Two patients recruited into the study had previously undergone stem cell transplantation. By chance these patients were randomly allocated to different interventions. However, it is apparent that in future studies in this population of patients should be stratified by whether or not they had received a previous transplant, as this may potentially affect the severity of mucositis experienced by the patient.

Prior to conducting the conducting the feasibility study, stratification by type of transplantation had been planned. The non-recruitment of patients receiving allogeneic transplantation, or an allogeneic transplant together with TBI means the success of stratification during the feasibility study cannot be assessed. The use of stratification increased the administrative burden of the feasibility study as three separate labels had to be produced and for the intervention and placebo groups to be packaged three separate times by Preston Pharmaceuticals. It is likely that the extra time that these processes necessitated may explain some of the delay experienced by Preston Pharmaceutical in dispatching the products to the hospital pharmacy, and therefore some of the delay in starting the trial. Kernan and colleagues (1999) recommend the identification of potential stratification factors through the use of multivariate analyses, such as those discussed in chapter two. However, as discussed in this chapter, there is

little consistency in these trials and more research in this area is needed before recommendations can be made. Allogeneic and TBI patients were excluded from the feasibility trial as a result of Clinician opinion; there is no indication that this patient group should be excluded from future trials of interventions for the prevention of mucositis. Also, in the case of small studies, it seems advisable to include type of transplantation as a stratification factor, due to the lack of consistency in the literature concerning the potential for the use of TBI to worsen mucositis severity (Avritscher et al., 2004).

9.11 Rates of withdrawal (attrition)

Prior to starting the trial, the expected rate of withdrawal for patients in this study was estimated to be 30% of the study population. This estimate was not based on the literature assessed for ROB, but rather on the experiences of the independent statistician who advised on aspects of the trial. Three patients withdrew during the study, giving a withdrawal rate of 33%. However, two of these patients elected to discontinue with supplementation, but allow the researcher to continue to visit them to perform daily assessments, resulting in only one patient (11%) withdrawing from the trial all together. This patient was withdrawn from the study due to her emergency transfer to the CCU with a chest infection.

Only 61 of 130 studies assessed for ROB gave information about drop-outs or withdrawals, with the remaining studies either stating that no patients withdrew or provided outcome data that matched the number of patients previously stated as randomised into the trial. There was also a large amount of variation in the number of withdrawals in these studies, with one study experiencing rates of withdrawal as high as 42% (Pfeiffer et al., 1990). Such high levels of withdrawal can introduce sampling bias, and affect the internal and external validity of the trial (Gul and Ali, 2010, Marcellus, 2004). Forty-three studies (33%) of the studies discussed in chapter four reported no withdrawals, which is a surprising result considering that these patients have cancer. However, similar results have been reported elsewhere in the literature: in a review of 87 longitudinal studies of organisational behaviour, Goodman and Bulm (1996) report that 38 studies (44%) provided no information about withdrawals. In contrast rates of withdrawal from trials as high as 70% have also been reported (Marcellus, 2004). It is

possible therefore that at least some of the studies assessed for ROB did experience drop-outs but that the authors chose to only publish the results of a sub-group of patients who completed the trial. The CONSORT statement, which aims to improve RCT reporting, recommends that, in addition to 35 other criteria, the numbers of patients recruited to each arm, withdrawals, and the reasons for such withdrawals are stated when the study is published (Schulz et al., 2010). While 21 of these studies assessed in chapter four were published before the CONSORT statement in 2001 (Altman et al., 2001), the remaining 22 studies are an area for concern. A 30% rate of withdrawal is a suitable expectation for a future study.

9.12 Compatibility with standard care

The feasibility trial was designed to be conducted over and above standard care. However, the unit did not have a mucositis prevention or treatment policy and patients were not given routine mouthcare advice. Only two patients enrolled in the study received any intervention for the prevention of mucositis: both performing oral cooling (cryotherapy) with ice during melphalan administration. However, only one of these patients received this intervention at the suggestion of a member of the clinical team, the other patient having read about the technique on the internet. Barker and colleagues (2005), identified substantial variation in standard care in a study which surveyed current oral care practices in 212 members of the Multinational Association of Supportive Care in Cancer (MASCC) or the International Society for Oral Oncology (ISOO) groups. Responses were received from 74 members (35%). The authors report a large amount of variation in the range and timing of oral hygiene measures and in the range of interventions prescribed for mucositis (Barker et al., 2005), and attribute the low response of this study to a lack of formalised oral care guidelines for patients undergoing cancer treatments at the non-responding institutions (Barker et al., 2005). However, this limited response rate, together with the fact that the authors do not provide information about which countries these responders came from, mean that the possibility that the results may be biased towards a practices in a particular country cannot be discounted. A lack of consensus in routine oral care strategies has also been identified in paediatric cancer centres (Glenny et al., 2004).

Benzydamine and Chlorhexidine were prescribed for the treatment of mucositis in the feasibility study on an *ad-hoc* basis. However, the use of neither drug is supported by either the Cochrane review for the treatment of mucositis (Clarkson et al., 2010), or the Multinational Association of Supportive Care in Cancer (MASCC) guidelines for the prevention and treatment of mucositis (Keefe et al., 2007). Patients in the feasibility study were also given a variety of other agents to "try out" including salt and soda mouthwash and Gelclair by the nursing staff. The only concession towards mouthcare witnessed by the researcher was that patients were occasionally given small pouches of saline to rinse out their mouths. However, this was often given with no instructions to the patient, or without the patient being informed of the importance of mouthcare.

Few studies assessed for ROB provided information about what standard care a patient received. Jack and colleagues (2010) reported in their review of supportive care in lung cancer trials that less than 50% of studies provided information about what constituted standard care; and when such care was described, it was often accompanied by statements about care being provided at the discretion of the treating doctor. This is a notable result as best supportive care is often used as a comparator arm in clinical trials, and a failure to properly quantify what this care actually entails may have significant ethical implications in trials (Jack et al., 2010), especially those which utilise a 'standard care' arm instead of a placebo or other control arm. The issue of standard care needs careful consideration before any future OM trial is conducted on this unit as the wide variety of interventions available to patients introduces confounding variables to the study results and the potential for bias.

9.13 Suitability of assessment instruments

A recent systematic review identified 57 oral assessment instruments used in either research or clinical practice (Gibson et al., 2010). Four of these assessment instruments were used in the feasibility trial. The instruments used to grade the oral cavity were the WHO score and the DIM, and were chosen after an extensive review of the literature. Overt differences were noticed between these instruments in the oral assessment data generated during the trial and these differences continued to remain after the subjective elements of the DIM instrument were removed. In one instance, the WHO instrument only showed that the patient remained to be ulcerative, while the data generated by the

DIM assessment instrument showed that the condition of the oral cavity was in fact improving. Both instruments produced data that showed similar trends, however it is clear that the DIM instrument provided a greater level of detail. These differences support the use of two assessment instruments in future trials, in order to provide as much information as possible about the condition of the oral cavity.

One patient, who ultimately did not consent to take part in the study, requested a demonstration of the oral assessment procedure during the initial approach by the researcher. When the researcher was talking the patient through the oral assessment process, and giving a physical demonstration, she noticed that the patient, who was Afro-Caribbean, had quite extensive racial pigmentation of the gingivae and mucosa, which would have made assessments of erythema (mucosal reddening) very difficult to conduct. Racial pigmentation is a common condition in people of Asian, African and Southern European descent with dark complexions (Webber, 2010). However, this issue does not currently appear to be reflected in the oral assessment literature.

The OMDQ was chosen to provide daily information about the levels of pain and diarrhoea experienced by the patient. The first question on this instrument asks the patient about their overall health. When completing this instrument for the first time, all patients in the trial answered with some variation of the response “I’ve got cancer”. The researcher therefore asked the patient to interpret this question as “how well are you feeling today”. A rewording of this question should therefore be considered before its use in any future trial and if any such amendment is made, this instrument should be revalidated. One patient got confused when asked to mark his response on the VAS scale for some questions and circle his response on a list of numbers for other questions. This problem was resolved when the researcher took the patient through the questionnaire question by question. In future studies, it may therefore be advisable to either ask patients to complete a sample copy of the questionnaire when they enter the study, or alternatively take the patients through the baseline questionnaire question by question.

The PG-SGA instrument was used weekly to assess changes in the patients' nutritional status. This instrument proved to be the most time-consuming, and arguably the least useful, instrument employed during the trial. As the PG-SGA is comprised of a large number of graded elements, changes in score can be due to a huge number of factors, resulting in results which are difficult to interpret. One of the variables scored in this instrument was patient weight loss; however, as patients received large amounts of fluids during the transplantation process, the weight losses experienced by patients were generally small. The last section of the instrument is an assessment of the amount of deficit in muscle and fat stores and whether a patient is experiencing fluid retention. Deficit was assessed over a number of different variables and the overall assessment then calculated, not by the addition of scores, but rather by the selection of an overall general score (no deficit, moderate or severe). This method of grading could therefore fail to reflect a large deficit in muscle or fat from one particular area of the body, because the rest of the patient is unaffected and the patient is therefore assessed as having an overall score of 'no deficit', resulting in the under-reporting of muscle or fat wastage. Furthermore, in order to complete the final section of this instrument, the researcher had to ask the patient to partially undress in order to make the assessments. In addition to the embarrassment for the patient, this process was time consuming, especially during the second week of treatment when the patient was very ill. Therefore, the PG-SGA instrument may be better utilised in trials which follow patients over long periods of time, instead of the three weeks it was employed in this study, and its use in any future study should be very carefully considered.

9.14 Weekend cover

The plan to conduct daily oral assessments in patients resulted in the researcher working seven days a week without a break for long periods of time. While this was feasible for a doctoral project, had more patients been recruited, or a second site opened, this situation would have become unworkable. Before starting the trial the researcher was promised that research nurses based on the ward would provide extra cover. However, the nursing staff in question were already managing extensive workloads from other trials and were either unwilling or unable to help. The most obvious option of dealing with this problem in any future trial would be to only conduct oral assessments on weekdays. However, this would result in a failure to capture the full picture of mucositis severity. Two of the patients recruited into the study became ulcerative towards the

second week of treatment, and remained ulcerative over the second weekend; but had experienced a resolution of their ulcerative symptoms by the time of their assessment on Monday. The use of weekday-only oral assessments for these patients would have precluded the accurate calculation of the days of ulcerative mucositis. In addition, the timing of conditioning chemotherapy commonly resulted in patients experiencing neutrophil and white blood cell count nadirs during the second weekend of treatment, occurrences which were associated with an increase in adverse events due to the risk of infections and febrile neutropenia. A lack of researcher cover during this period could result in adverse events being underreported and in the worst case scenario, a delay to the reporting of serious adverse events to the proper authorities.

The provision of holiday cover was another issue that the researcher struggled to organise. Patients continued to be scheduled for transplantation over the Christmas holidays, and while both eligible patients admitted just prior to Christmas declined to take part in the trial, had they given consent, the researcher would have had to continue daily visits during the holidays. Clearly, for future studies it is not feasible for one researcher to conduct daily patient visits seven days a week, and a second researcher will have to provide some mid-week or weekend cover. In any future trial which necessitates daily assessments and therefore weekend and holiday cover, this cover should be formally organised before the commencement of the project, and inter-rater reliability testing should be conducted to ensure accurate reporting.

9.15 Researcher support

The seven day a week nature of the data collection process had a considerable impact on the researcher, who was a relative research novice. The patients recruited into this trial, like the rest of the patients on the ward, were very ill during the transplantation process, and the researcher found this quite difficult to deal with at times, especially during data collection periods in which she could foresee no chance for a day off. While the researcher had attempted to mentally prepare herself for severely ill and distressed patients, she found that she was unprepared for dealing with the distress of patients' families. The rotational nature of nursing shift patterns resulted in the researcher often being the only person a patient was seeing consistently on a day-to-day basis, and therefore the families, and the patient themselves, often looked to the researcher to

provide support and reassurance about whether or not a particular symptom experienced was ‘normal’. This situation often caused the researcher to feel distressed.

Research into physiological distress in cancer researchers is limited; however, some research has been in oncology nursing staff (Grulke et al., 2009). Grulke and colleagues (2009) conducted a prospective study using questionnaires to compare reports of emotional distress in allogeneic transplantation patients to that of their nurses. The authors reported a significant correlation between the patients and nurses in the level of distress experienced during transplantation ($P<0.001$) (Grulke et al., 2009). Other studies have reported that one-third of cancer nurses suffer from a clinically-relevant level of distress associated with their job (Catalan et al., 1996) and that caring for cancer patients negatively impacts the quality of life of oncology nurses (Ergun et al., 2005). It could be hypothesised that the levels of distress experienced by researchers working in oncology may be higher than those experienced by cancer nurses, as the researcher may experience additional stress by being unable to help the patient in any way.

The researcher often found that during patient visits she was performing tasks that were outside her role as a researcher, such as helping a patient to perform mouthcare, or holding a sick bowl for a patient who was overcome with nausea. However, the researcher recognised that such practices are all part of the nature of research, and that after she had listened to the patient’s views about the program currently on television, the patient was often more amiable to the oral assessments or a discussion about their current levels of diarrhoea or vomiting, discussions some people might find quite personal. However, this additional time spent with the patients also increased the levels of distress felt by the researcher, especially when she could do nothing to help with the situation. The researcher found that speaking to the nursing staff, her friends, and her supervisors about these distressing episodes helped her to deal with them. However, future trials conducted in this area should aim to provide researcher support and an outlet for discussion of the issues that researchers find particularly distressing.

9.16 Initiation of study intervention

Four patients missed their first dose of study medication. This delay in starting the trial was due to a lack of beds precluding hospital admission for two patients, and an oversight by nursing staff in one patient. The remaining patient missed his first dose due to a slight cough, which delayed a decision regarding his suitability for transplantation until ward rounds the next morning. As the researcher experienced many problems with consenting patients for the trial and organising pharmacy release on the day of patient admission to the ward, the possibility of patients first using the intervention or placebo on the day after admission to hospital should be considered in any future trial.

There appears to be little consistency in when interventions were started in the studies assessed for ROB earlier in this thesis. Interventions can be roughly separated into those which are initiated at the start of treatment and administered at approximately the same time as therapy, such as cryotherapy or amifostine, and those which were not. However, this distinction becomes even more inexact when glutamine is considered, as there is substantial heterogeneity in terms of dose, scheduling and administration in the trials included in the prevention review for this intervention (Worthington et al., 2010), meaning that glutamine could therefore be classified in both groups. Among interventions not administered at the same time as therapy, there appears to be no rationale for the timing of starting intervention or placebo, with initiation at 24 hours before therapy (Jebb et al., 1994, Shieh et al., 1997), three days before therapy (Choi et al., 2007, Kaul et al., 1999), seven days before transplantation (Labar et al., 1993), seven days before therapy (Shieh et al., 1997) and two days after transplantation (day+2) (Oberbaum et al., 2001) all being reported. Therefore it makes practical sense to select a starting point which is realistic for the researcher to achieve, in this case starting the trial on the day after hospitalisation.

9.17 Feasibility of stopping points

Patients ceased supplementation when three consecutive days of grade one mucositis were recorded as assessed using the WHO instrument. A miscount of the number of days that patient 3 had a WHO score of below grade two led to an extra day of assessment in this patient, but not an extra day of supplementation as the patient had neglected to take the previous days dose. This miscalculation took place because it was

a weekend and the researcher did not have access to the previous week's oral assessments, which had been filed and locked away in an office in a department that was not open over the weekend. Unable to check the notes, the researcher asked the patient if she could remember when she was last ulcerative. Unfortunately, the time point given proved not to be correct. The researcher learned from this experience and the mistake was not repeated. For all future patients that were close to finishing the trial and were seen on a weekend, a note was made in the researcher reflective diary detailing their previous two WHO scores.

One patient did not develop ulcerative mucositis. The possibility that this may happen was not considered when the protocol was written due to the expected incidence of mucositis in this high-risk patient population. In this case, the researcher and her primary supervisor decided that the patient should receive supplementation for 15 days and then exit the study, as it was stated in the study protocol that patients would be expected to receive supplementation for approximately 15 days. Two patients withdrew from the study due to adverse events unconnected to the placebo or intervention employed in the trial. One patient withdrew due to nausea and vomiting. The other patient because of flu-like symptoms during chemotherapy which were suspected to be the result of a Hickman line infection. Both these patients gave verbal consent for the researcher to continue to follow them up and perform daily oral and pain assessments and weekly nutritional assessments. Due to the lack of a formal stopping rule for these patients, patients were followed up until they had reached the formal stopping rule for patients receiving the intervention or placebo, namely, three consecutive days of grade one mucositis.

In future trials stopping rules need to be written for both patients who do not become ulcerative and those patients who stop the trial early but give consent for follow-up. For patients who do not become ulcerative, it is difficult to decide an appropriate cut-off based on the number of consecutive WHO scores, because of the possibility that a patient may experience delayed mucositis development. Therefore, the previously used cut-off of 15 days of supplementation seems appropriate. For patients who withdraw but give consent for follow-up, the cut-off of three consecutive days of grade one mucositis allows for direct comparison with other patients, and therefore seems suitable. The

possibility that patients may be discharged with ulcerative mucositis was also not considered when writing the protocol, and this should also be included as a stopping rule.

The feasibility trial did not employ formal stopping rules for stopping the study. Early stopping due to an apparent benefit in clinical trials introduces bias into the results (Higgins and Altman, 2009), and was identified in one study assessed for ROB in chapter four (Loprinzi et al., 1990). Greater effect sizes have been identified in RCTs stopped early when the intervention of interest has shown an apparent benefit (Bassler et al., 2010). In addition, beneficial effects identified early on in a study have been shown to have vanished by the completion of the study (Abraham et al., 2003), suggesting that such an effect was down to chance (Heffner et al., 2007). If future studies employ formal trial stopping rules, such rules should only allow for the cessation of recruitment when the evidence is vast and a sufficient number of patients have been recruited into the study, in order to avoid a result caused by chance (Heffner et al., 2007).

9.18 Dose and suitability of application method

The dose chosen for this study was determined by what was available from Healthplus. However, as a variety of vitamin E doses have been used in patients receiving chemotherapy, it is possible that the dose used in any future trial may need to be reassessed depending on formulation and availability. The suitability of the method of applying the intervention or placebo was not measured quantitatively during this study, which may have been an oversight. However, patients did provide anecdotal feedback to the researcher during the daily assessments and this was recorded in the researcher reflective diary. Four patients reported that the gelatine capsules were difficult to break. However, this issue was resolved after discussion with the researcher, who recommended patients use their molars, rather than their incisors, to break the capsule. One patient (Patient 3) detested the taste of the capsule, and removed it from her mouth before swishing and expectorating the solution.

The mode of application was chosen because it had been used in a previous vitamin E trial (Ferreira et al., 2004), and the authors of that study did not comment on patient agreeability with the capsules. In the Sung and colleagues study, rather than using a gelatine capsule, the vitamin or placebo mixture was dissolved in an oil vehicle and then used as a mouthwash (Sung et al., 2007), which may be a more appropriate method of applying the intervention. In addition, to the mode of application, the texture of the intervention and placebo capsules was a problem for some patients, particularly those suffering from nausea and vomiting. Since completing the feasibility study, the researcher has become aware of another study which employed vitamin E for the prevention of mucositis in patients undergoing allogeneic transplantation. This study, which recruited 60 patients, was conducted in Iran, and was published in a journal which only recently became available on the Medline literature search engine. The authors reported that there was no difference between the groups in the incidence of mucositis experienced by patients, but that more trials were warranted (Ghoreishi et al., 2007). Future trials should carefully consider both the suitability of the mode of application and the texture or consistency of the intervention.

9.19 Adverse event reporting

Doses of vitamin E of up to 3200iu have not been associated with consistent adverse events (Kappus and Diplock, 1992). Adverse events previously reported with high doses of vitamin E, which are mainly derived from case-reports or uncontrolled studies, include gastrointestinal (GI) distress, muscle weakness, mild creatinuria, elevated serum creatinine kinase, and elevated serum triglycerides. Of these events only gastrointestinal distress and elevated creatinine kinase were experienced by patients, and both these adverse events were also experienced by patients on the placebo control arm. No obvious difference between the arms was detected; however, statistical testing was not conducted due to the low numbers of patients recruited into the trial.

Data were collected prospectively on all new side effects (adverse events) experienced by patients in the trial from the date of consent until 30 days after the last dose of intervention or placebo. All three sets of patient notes were viewed daily by the researcher, who was blind to the treatment allocations. In addition, patients were asked to report the number of episodes of diarrhoea and vomiting and nausea to the researcher

during their daily oral assessments. Adverse events were discussed with the consultant Clinician to determine whether an event was 'normal' during transplantation. Adverse events were graded using the common terminology criteria for adverse events version 3 (Cancer Therapy Evaluation Program, 2003). Consequently, adverse event reporting took up a considerable amount of the researcher's time. It is notable that the unit research nurses recorded adverse events retrospectively on a weekly basis in trials running concurrently with the researcher's trial. Such a method of retrospective weekly adverse event reporting is an option for future trials, however, there is the possibility that events may be overlooked and therefore underreported. In addition the use of weekly reporting has the potential to take up a whole day of a researcher's time and may result in a backlog of adverse event reporting if a researcher's plans were changed at short notice.

One serious adverse event (SAE) was recorded during this trial. This was a chest infection which was serious enough to necessitate the transferral of the patient to the critical care unit. This patient went on to make a full recovery. Patient 2 also experienced the greatest number of adverse events of any patient during the trial. Due to the low numbers of patients recruited during the trial, no statistical tests were used to analyse differences between the arms for the numbers or types or adverse event experienced by patients. While, it does not appear that patients in the vitamin E arm of the trial experienced adverse events of a greater number or severity than those in the placebo arm, the safety of vitamin E in this patient population remains unproven by this study.

Only 62 studies assessed in chapter four reported adverse events, and there was no consistency in how such events were reported. Trotti and Bentzen (2004), reviewed event reporting in nine frequently cited head and neck studies and found that four different grading scales were used in these studies. The number of acute effects reported by these studies ranged from three to ten, with mucositis and neutropenia being the only two adverse events reported consistently by these studies (Trotti and Bentzen, 2004). Such a lack of consistency makes the comparison of treatments difficult, which in turn prevents patients being properly informed about the risks of a particular treatment. In addition, such a haphazard method of reporting events may result in late effects being

under-reported and introduces bias to the results (Trotti and Bentzen, 2004). When adverse events are reported, some studies do not report data for all randomised patients, instead reporting only those events which affect a certain number, or percentage, of patients, or reporting data as events rather than patients (Ioannidis et al., 2004). An extension to the CONSORT statement was published in 2004 which provides ten recommendations for adverse event reporting in clinical trials, these include: that events should be defined; that methods and timings of assessment should be explained and that any methods of analysis used should be described in the statistical methods; that withdrawals due to events should be stated and explained and that events should be described in terms of absolute risk; that sub-group analyses should be stated and described; and that the benefits and harms of a particular intervention should be discussed in detail (Ioannidis et al., 2004). It appears however, that such recommendations are yet to be adopted for the reporting of adverse events in mucositis clinical trials. In order for short term benefits, in terms of mucositis prevention, to be compared to longer term outcomes, such as event-free survival, better adverse event reporting in future mucositis prevention trials is crucial.

In such future trials the time spent recording adverse events could be reduced by the inclusion of expected events relating to the transplantation process in the investigator brochure or protocol. This was not done for feasibility trial as the researcher was initially unsure what these events would be. These expected results are shown in Table 26.

Table 26: Expected Adverse Events in a Future Trial in Stem Cell Transplant Patients

Category	Event
Blood / bone marrow	Reduction in white blood cell count (WBC)
	Reduction in platelet count
	Reduction in haemoglobin count
	Reduction in red cell count
	Reduction in neutrophil count
	Reduction in monocyte count
	Reduction in eosinophil count
	Reduction in lymphocyte count
	Reduction in basophil count
	Reduction in MCH and MCHC count
Gastrointestinal	Nausea
	Vomiting
	Diarrhoea
Dermatology/ skin	Alopecia
Infection	Febrile Neutropenia

9.19.1 Suitability of 30 day after last dose AE reporting

Adverse events were collected throughout the study from the first day of supplementation until 30 days after the patient had received their last dose. However, after a patient had been discharged from hospital the recording of adverse events proved problematic. When the patient attended outpatients appointments adverse blood values were recorded from the patient's electronic notes. The patient was also asked by the researcher to verbally detail any problems they may currently be experiencing, or had experienced since leaving hospital. It is likely the method of adverse event reporting used after patient discharge in this trial resulted in the underreporting of adverse events. However, it is difficult to determine whether alternative methods of adverse event reporting would be more appropriate in any future study. These reporting problems were compounded by the referral of non-locally based patients to their local hospital for follow-up, in an attempt to reduce the amount of travelling they would have to undertake. All of the patients in question were seen in hospital by the researcher within 30 days of their last dose of intervention or placebo, and adverse events were recorded at this visit. However, such referrals may delay expedient reporting in the event of a SAE.

One potential approach to recording adverse events in the discharged patients would be to ask patients to record events experienced after discharge in a patient diary. However, poor compliance with patient diaries has previously been reported (Stone et al., 2003). Stone and colleagues (2003), investigated patient compliance with paper diaries compared to electronic diaries in patients experiencing pain episodes. Patients were asked to complete these diaries at set times three times a day for 21 days. The ingenious inclusion of photosensors in the binder enclosing the paper diaries allowed the researchers to compare reported compliance (the number of pages of the diary completed) to actual compliance (the number of times the diary was opened) for diary completion and then calculate the amount of compliance faked by patients using this method of data collection. The reported compliance in the paper diary group was 90.5%. However, when data from the photosensors were included, actual compliance was only 10.9%, indicating that 79.5% of all patient paper diary entries were faked (Stone et al., 2003). In contrast, the rate of compliance for the group of patients using electronic diaries was 93.6%, and as the software for the electronic Palm computer only allowed a diary entry during a 30 minute window for each set data collection time point, this much higher rate of compliance with electronic methods of data collection appears to be genuine (Stone et al., 2003). The use of electronic methods to collection data after patients have been discharged from hospital, either through handheld computers or mobile phones has many potential benefits, namely that it would allow adverse events, self-reported oral mucositis scores and side effects such as taste changes to be tracked overtime, and reduce the likelihood that adverse events were underreported after discharge from hospital. The use of electronic methods of data collection is therefore a possibility for future trials. However, such a study would have to be supported by a large grant to cover the set-up and running costs of such a system.

Another lower cost method of ensuring adequate adverse event reporting in discharged patients would be for the researcher to follow the patients up by phone on a weekly basis. However, this method may be problematic as the myeloma nurse also typically follows recently discharged transplanted patient up by phone between outpatient appointments, and therefore there is the potential for patients to under-report problems because they feel that they have already told someone about a particular symptom. Therefore reported symptoms would need to be cross-referenced between the researcher and the myeloma nurse. Alternatively, patients could be asked to retrospectively

complete a tick-sheet of adverse events when they attend an outpatient appointment. Adverse event reporting in the discharge patient is therefore problematic for any study. The method of reporting used in this trial for discharged patients was feasible and could be used in future trials, however, the use of alternative methods, such as phone calls, electronic devices or tick-sheets of symptoms, could be used in addition in an attempt to minimize under-reporting of events.

9.20 Recommendations for future trials

The results of this feasibility study have been used to make recommendations for future studies of pharmacological interventions for the prevention of OM. These are shown in Table 27. The low number of patients recruited into this study precludes any recommendation being made on the suitability of vitamin E used for the prevention of mucositis.

Table 27: Recommendations for Future Trials of Pharmacological Interventions for the Prevention of Oral Mucositis in Patients Undergoing BMT

Item	Recommendation
Approvals	
Regulatory approvals	At least a year should be set-aside for gaining the necessary approvals prior to starting the study.
Professional relationships	
Relationship with Clinicians	Clinicians from the unit should be consulted early during the trial design process in order to work through any potential problems voiced.
Relationship with support staff	Good working relationships between research staff and support staff should be enthusiastically encouraged.
Trial registration	
Registration of clinical trials	Trials should be registered prior to starting recruitment. This will minimise publication bias and the selective reporting of significant findings in publications. In addition, this will avoid unnecessary duplication of trials, and ensure that healthcare decisions are made after consideration of all available evidence.
Randomisation	
Randomisation	Adequate descriptors of randomisation processes need to be included in future publications.
Stratification	
Stratification	Patients should be stratified by type of transplant (autologous/ allogeneic), type of conditioning (TBI/no TBI) and by history of previous transplant (yes/no).
Allocation concealment	
Allocation	Adequate allocation is essential and should be employed in

Item	Recommendation
concealment	future mucositis studies. Appropriate methods of allocation concealment include sequentially numbered drugs containers of identical appearance and pharmacy controlled randomisation.
Blinding and allocation concealment	
Blinding	Future trials should employ adequate blinding. In studies in which blinding of patients cannot be achieved, such as the cryotherapy or honey studies assessed for ROB, blinding of outcome assessors is essential. There is no reason why adequate outcome assessor blinding cannot be organised if the trial is set-up carefully.
Assessments	
Oral assessments	Daily assessments of the oral cavity should be performed using an appropriate assessment instruments. Both a simple scale and a multi-component instrument should be employed to provide the greatest possible amount of information about the oral cavity, and facilitate inclusion of the results of the trial in meta-analyses. Researchers should select an instrument that is validated, acceptable to patients, and suitable for their chosen population. Therefore no recommendation of specific instruments is made. If more than one researcher is to conduct the oral assessments then inter-observer reliability should be calculated before data collection commences.
Timing of assessments	Future studies need to have a clear rationale for the timing of oral assessments. Oral assessments should be conducted frequently enough to identify oral changes, but not frequently enough to burden the patient unduly. The use of daily oral assessments is recommended.
Pain assessments	If the OMDQ instrument is used in a future trial, the first question should be reworded and the instrument revalidated
Staffing	
Weekend cover	Cover should be organised to provide adequate breaks for researchers
Researcher support	Future studies should consider the psychological impact of working in oncology on the researcher and provide support accordingly
Outcome reporting	
Outcome reporting	Future studies should attempt to avoid reporting selective outcomes, such as the incidence of severe mucositis. Full reporting of pre-defined outcomes would ensure a large pool of eligible studies for inclusion in future editions of the Cochrane prevention review.
Adverse event reporting	
Adverse event reporting	Adverse event reporting should be performed prospectively. Appropriate methods of recording adverse events from patients who have been discharged from hospital should be considered and written into any future protocol.
Standard care	
Standard care	In studies conducted over and above standard care, attempts should be made to standardise care on the unit before starting the trial.
Stopping points	

Item	Recommendation
Stopping points	Appropriate stopping points should be written into the protocol for patients who withdraw from the study early but continue to be assessed by the researcher, as well as for patients who do not become ulcerative.
Rates of recruitment	
Expected rates of recruitment	Single site studies should expect to recruit a mean of 0.78 patients a week[41]. Recruitment should be planned accordingly.
Rates of withdrawal	
Expected rates of withdrawal	Rates of withdrawal in future studies can be expected to be approximately 30% of all patients randomised.
Publication	
Publication	Authors should follow the CONSORT guidelines when writing up their results for publication.

9.21 Conclusion

This chapter has discussed various issues identified in the previous chapters of this thesis. The feasibility trial was conducted as a full 'dummy' study using the same randomisation, allocation concealment, pharmacy release and data collection procedures as could be employed in a full study, and although the pre-stated number of patients were not recruited into the feasibility study, the results can still be used to inform future studies about a variety of important issues including expected recruitment rates, expected lengths of delays in obtaining regulatory approval and the potential issues that could be experienced when attempting to recruit patients into a study. Adequate blinding and allocation concealment were proved to be possible, through the use of sequentially numbered drugs containers of identical appearance, central allocation and the protection of the randomisation sequence from the outcome assessor. The use of outcome assessor blinding was proven to be possible even in small studies conducted by one member of staff. There is therefore no reason why outcome assessor blinding could not be employed in future studies trialling interventions, such as cryotherapy, in which blinding of patients is not possible. The results of the feasibility study also add to the literature on the lack of consistency in standard care for mucositis prevention. This issue needs to be addressed urgently to close the gap between research and clinical practice.

[41] Mean of the rates of recruitment in single site studies included in the Cochrane OM prevention review together with the rate of recruitment experienced in the vitamin E study.

Adverse event data collected during the feasibility study can be used to produce lists of expected adverse events in future trials, which should help reduce the amount of AE reporting in such trials. Omissions in adverse event reporting were identified as an issue in some of the studies included in the Cochrane prevention review. Such omissions are troublesome for researchers planning future studies, and may prevent the intervention in question being adopted into clinical practice. Conducting a feasibility trial before full data collection should be considered when designing future trials.

9.22 Skills learned during the Doctoral programme

- Significant insight into designing, setting up and conducting clinical trials
- Knowledge of the regulatory approvals process
- An insight into methodological issues in clinical trials
- Knowledge of statistical testing, particularly the use of meta-analyses
- Improved writing skills
- Public speaking
- Teaching experience
- Good clinical practice training
- Time management
- Project management
- Interpersonal skills

Chapter 10 Conclusion

Oral mucositis is a painful and distressing side effect of therapy for cancer, which exerts a substantial economic and clinical impact, and negatively affects patient quality of life. Despite research into the pathogenesis of mucositis, the identification of treatment and patient related risk factors which may affect its development and a considerable amount of time and effort spent identifying and trialling interventions which may prevent or treat the condition, mucositis still represents a significant treatment-related toxicity.

Various interventions have been trialled for the prevention of mucositis. Such interventions have varied in cost and complexity from the low cost 'low tech' use of ice chips during chemotherapy administration, at one end of the scale, to the use of growth factors in complex schedules at considerable cost, at the other. However, a consistent benefit of any particular intervention has yet to be demonstrated. The three interventions found to be beneficial in the 2010 update of the Cochrane prevention review at all three dichotomies of interest-keratinocyte GF, honey and cryotherapy-all have drawbacks either in terms of costs and adverse events, or the quality of the evidence, due to their lack of outcome assessor blinding. Fifty-seven oral assessment instruments were identified in the systematic review of orals assessment instruments shown in chapter five of this thesis. The multiplicity of oral assessment instruments available for the assessment of mucositis and the variation in what these tools actually measure has hampered the inclusion of studies, or entire interventions, into systematic reviews, including the Cochrane review of interventions for the prevention of mucositis. While this has been partially addressed by the inclusion of some studies in a 'text only' format in the recent update of the review (Worthington et al., 2010), a considerable number of studies were still excluded either because of an inappropriate method of assessment, or because data are presented in a format incompatible with the incidence by grade of mucositis measures used in the review. Vitamin E was identified in this thesis as one such intervention, with conflicting results reported by trials investigating the use of this supplement for mucositis prevention.

A sensitivity analysis was conducted on the results of the Cochrane prevention review update, and showed that the results of the review were substantially changed if studies assessed to be at unclear or high risk of bias were excluded. The literature from the

prevention review was then assessed to determine how they could be used to inform future studies. A lack of consistency was identified in both the timing of oral assessments used in these studies, and the other outcomes reported by these studies. Adverse event reporting was also highlighted as an area of concern, as although was the most frequently reported of all outcomes, fewer than 50% of the trials included in the review update providing information about side effects.

The issues surrounding conducting a trial of vitamin E for the prevention of mucositis were explored in a feasibility study. This feasibility study employed sequentially numbered drugs containers which were identical in appearance and pharmacy release, to protect the allocation schedule, and ensure adequate allocation concealment and outcome assessor blinding.

This thesis has combined appraisal of the literature with empirical research and has used lessons learned from previous studies, together with the results of the feasibility study to identify best practice recommendations for future trials of interventions for the prevention of mucositis. Although low numbers of patients were recruited into the feasibility study, a problem which was mainly due to a lack of willingness of the Clinicians on the unit to allow their patients to participate in the project, and personnel dynamics between the Clinicians themselves, the results of this feasibility trial, allow for 19 recommendations for conducting future trials to be made. These include that future trials should allow at least a year to gain all the necessary regulatory approvals prior to starting the trial. Clinicians from the unit should be contacted early in the design of the study and asked for their input and any objections to the trial so that such issues can be resolved before regulatory approvals are made. Blinding of outcome assessors and adequate allocation concealment should be used in all future trials, and if such trials are to be conducted in a group of patients receiving a mix of different transplants, then stratification by type of transplant should be employed.

The feasibility trial identified a difference between the oral assessment instruments employed during the trial, suggesting that authors of future trials need to think carefully about which instruments they employ, and the timing of these assessments. In addition

it was found that adverse event reporting, although crucial for patient safety, took up a significant amount of the researcher's time. The data generated from the adverse event reporting has been used to suggest expected adverse events associated with BMT treatment, which could be written into the protocol for future trials, and would therefore reduce researcher burden in studies which stipulate that expected events do not have to be recorded. In future trials adverse event reporting should be conducted prospectively.

The feasibility study identified a lack of consistency in the standard care employed on the unit, a problem which has been identified elsewhere in the literature. Attempts should be made to standardise care on units where this is a potential problem prior to starting recruitment. Finally attention should be given to the writing up of the results of the trial for publication. The manner of randomisation should be described in full and the authors should avoid the reporting of selective outcomes. Authors should follow the CONSORT guidelines when writing their report.

The clinical and economic impact of mucositis, together with the devastating effect of mucositis on the patient, indicates that trials of new interventions, together with trials which confirm the results of existing interventions, are crucial. It is hoped that the experience and findings of this thesis can be used to guide researchers working on future trials of interventions for the prevention of mucositis. Such trials need to be conducted and reported as rigorously as possible in order to be beneficial for future patients.

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Appendices

Appendix 1

Example ROB assessment.

Study assessed to be at:

- low overall ROB,
- low ROB for allocation concealment

Author (date)	Intervention	Adequate Sequence Generation?	Allocation Concealment	Blinding			Incomplete Outcome Data Addressed?	Free of Selective Bias?	Free of other bias?
				Carer blinding	Patient blinding	Outcome assessor Blinding			
Dazzi et al, 2003[42]	GM-CSF	Unclear Quote: "…were randomly allocated to the GM-CSF or the placebo group" Comment: random component not described.	Yes Quote: "Study suspensions were prepared by the pharmacy unit and provided to the bone marrow transplant patients." Comment: Pharmacy controlled randomisation.	Yes Comment: Intervention and control were dispatched from pharmacy, unlikely that carers would have knowledge of allocation.	Yes Quote: "double blind"	Yes Quote: "double blind"	Yes 90 patients randomised. ITT analysis used. No missing outcome data.	Unclear Data presented for incidence of stomatitis, incidence and duration of severe stomatitis, and patients judged maximum mucositis score (table 3)	Yes Study appears to be free of other sources of bias

- low ROB for outcome assessor blinding

[42] Dazzi et al, 2003, p560,

Appendix 2

Search strategy employed for systematic review of oral assessment instruments

1. exp NEOPLASMS/
2. neoplasm$.mp.
3. cancer$.mp.
4. tumo?r.mp.
5. malignan$.mp.
6. exp RADIOTHERAPY/
7. radioth$.mp.
8. exp CHEMOTHERAPY/
9. chemoth$.mp.
10. BONE MARROW TRANSPLANTATION/
11. ("bone marrow" and transplant$).mp.
12. or/1-11
13. ORAL HYGIENE/
14. MOUTH DISEASES/ OR CANDIDIASIS, ORAL/ OR ORAL MANIFESTATIONS/ OR ORAL ULCER/ OR STOMATITIS/
15. mouthcare.mp.
16. 'mouth care'.mp.
17. 'oral hygiene'.mp.
18. SEVERITY OF ILLNESS INDEX/
19. OBSERVER VARIATION/
20. NURSING ASSESSMENT/
21. REPRODUCIBILITY OF RESULTS/
22. or/13-17
23. or/18-21
26. 12 and 22 and 23

(UKCCLG-PONF, 2006)

Appendix 3

Oral assessment instruments

Daily Index of Mucositis (DIM)

Table 2. Guide for the evaluation of mucositis

		Grade 0	Grade 1	Grade 2	Grade 3
Lips	Aspect	Smooth, soft	Slightly wrinkled	Rough	Tumefied, cracked Ulcerated, bleeding
	Colour	Pale pink	One to several reddened zones	Red, several inflammatory zones, one zone of desquamation	Red, bleeding
	Dryness	Humid	Slightly dry	Dry	Cracked
Gingiva	Aspect	Smooth, glossy	1 to 2 inflammatory zones or 1 to 2 white plaques	Whitish coating Desquamation Inflammatory zone (10–50%)	Ulceration + edema + bleeding
	Colour	Pink	Pale	Red	Shiny red
	Dryness	Humid	Slightly dry	Dry	Bleeding
Buccal Mucosa	Aspect	Pink, smooth	1 to 2 inflammatory zones 1 to 2 white plaques (20%)	Tumefied White coating Desquamation (10 to 50%)	Bleeding, ulceration Inflammation (>50%) + edema White plaques
	Colour	Pink	Pink with some red zones	Red (>20%)	Dark red
	Dryness	Humid	Slightly dry	Dry	Ulcerated
Tongue	Aspect	Firm prominent papilla	White coating Prominent red papillae Inflammatory zones Marked median line	Heavy tumefied base Prominent red papillae	Heavy, thick, tumefied Ulcerated, streaked
	Colour	Pink	Pink with red or white zones	Entirely red with even red papillae	Extremities dark red White coating Vesicles, black ulcers
	Dryness	Humid	Dry Hardly mobile and painful	Very dry and tumefied	very dry and rough
Swallowing		Normal Good mastication No constraint	Constraint in mastication and swallowing (conscious gesture)	Difficult Impossible to swallow solid food	Absence of swallowing and/or mastication (saliva spit)
Saliva		Fluid, light	Increased	Thick and viscous	Rare Mouth dry
Voice		Normal	Slightly changed	Raspy and deep	No longer talks
Pain		Absence	Moderate	Need for minor analgesics	Need for major analgesics

(Tardieu et al 1996, Permission Granted)

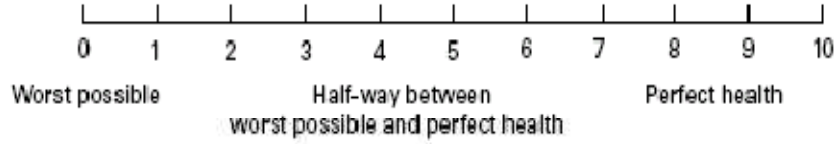
World Health Organisation (WHO) instrument

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WHO Anon, 1979	"None"	"Soreness and erythema"	"Ulcers, erythema. Patient can swallow solid diet"	"Ulcers, extensive erythema. Patient cannot swallow solid diet"	"Mucositis to the extent that alimentation is not possible"

(Anon, 1979)

Oral Mucositis Daily Questionnaire (OMDQ)

1. How would you rate your OVERALL HEALTH during the PAST 24 HOURS?
(circle one number)



2. During the PAST 24 HOURS, how much MOUTH AND THROAT SORENESS did you have?
(circle one number)

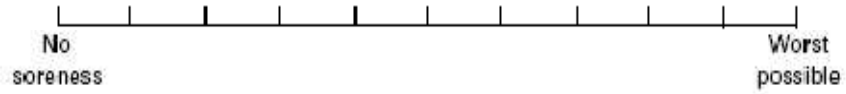
No soreness 0
A little soreness 1
Moderate soreness 2
Quite a lot of soreness 3
Extreme soreness 4

If you circled 0, please skip to question 5

3. During the PAST 24 HOURS, how much did MOUTH AND THROAT SORENESS limit you in each of the following activities?
(circle one number)

	Not Limited	Limited A Little	Limited Some	Limited A Lot	Unable To Do
a. Swallowing	0	1	2	3	4
b. Drinking	0	1	2	3	4
c. Eating	0	1	2	3	4
d. Talking	0	1	2	3	4
e. Sleeping	0	1	2	3	4

4. On a scale of 1 to 10, how would you rate your OVERALL MOUTH AND THROAT SORENESS during the PAST 24 HOURS? *(circle one number)*

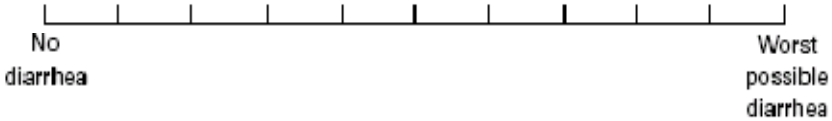


5. During the PAST 24 HOURS, how much DIARRHEA did you have?
(circle one number)

No diarrhea 0
A little diarrhea 1
Moderate diarrhea 2
Quite a lot of diarrhea 3
Severe diarrhea 4

If you circled 0, STOP here

6. On a scale of 1 to 10, how would you rate your OVERALL DIARRHEA during the PAST 24 HOURS? *(circle one number)*



(Stiff et al, 2006, Permission Granted**)**