Abstract of dissertation entitled

“Evidence-Based Intervention Protocol of Using Ice Water Mouthwash in the Prevention of Stomatitis for Patients Undergoing Autologous Haematological Stem Cell Transplantation”

Submitted by

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for the degree of Master of Nursing

at The University of Hong Kong

in August 2013
Haematological stem cell transplantation (HSCT) is a revolutionary treatment for haematological malignancies. Although HSCT is potentially curative, patients usually develop stomatitis which is a common and debilitating complication after the transplantation. Furthermore, stomatitis may predispose patients to various complications which are associated with significantly increased morbidity and mortality.

In some studies, ice water mouthwash has been shown to be an effective method for the prevention of stomatitis. However, a high-level evidence-based protocol on the prevention of stomatitis has not been fully developed and it is not commonly practiced in most HSCT centers at present. A well established protocol can help to minimize the patients’ suffering and avoid prolonged hospitalization. The nurses who are involved in patient education, assessment, care for, and coping with stomatitis, play an important role to bring these innovations into practice.

In this regard, this translational research aims at developing an evidence-based protocol on using ice water mouthwash in the prevention of stomatitis for patients undergoing autologous HSCT. A systematic search for relevant literatures was performed with the use of five electronic databases. Six relevant studies were found. Critical appraisal on the relevant studies was conducted. The level of evidence extracted from the studies was graded according to the Scottish Intercollegiate
Guidelines Network (SIGN) and were synthesized to establish the protocol for patients in the proposed setting. The implementation potential of the protocol was assessed in terms of the transferability, feasibility, and cost benefit ratio. An implementation and evaluation plan was established for comprehensive evidence-based protocol development.

The successful implementation of the protocol will be beneficial for the patients undergoing HSCT as it may hasten their recovery, shorten their hospital stay, and minimize their distressing experience and suffering.
“Evidence-Based Intervention Protocol of Using Ice Water Mouthwash in the Prevention of Stomatitis for Patients Undergoing Autologous Haematological Stem Cell Transplantation”

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A dissertation submitted in partial fulfillment of the requirements for the Degree of Master of Nursing at The University of Hong Kong August 2013
Declaration

I declare that this thesis represents my own work, except where due acknowledgement is made, and that it has not been previously included in a thesis, dissertation or report submitted to this University or to any other institution for a degree, diploma or other qualifications.

Signed ....................................................................................................

Ng Yuen Man
Acknowledgements

I would like to express my sincere gratitude towards Dr. William Li, my dissertation supervisor, for his professional advice and unreserved support in helping me to complete this dissertation. I would also like to thank the teachers in this master study that enlightened my vision for the future.

I am also grateful to my family, friends, classmates and my fellow colleagues who shared my happiness and encouraged me throughout my whole masters study.
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Chapter 1: Introduction

1.1 Background

In Hong Kong, more than a thousand patients are diagnosed with haematological malignancies every year (Red Cross, 2012). The prognosis of these patients is usually poor with conventional treatment strategies such as chemotherapy and radiotherapy depending on disease grading and stage. Haematological stem cell transplantation (HSCT) is a potentially curative procedure that revolutionized the treatment of haematological malignancies. The major phases of HSCT include the conditioning phase, the infusion of the haematopoietic stem cells, the pre-engraftment phase, and the post-engraftment phase. At the start of HSCT, conditioning with myeloablative chemotherapy agents such as cyclophosphamide, busulfan, melphalan, and cytarabine, with or without total-body irradiation, are used to eradicate the malignant cells in the patient’s body (Niscola, Romani, Cupelli, Scaramucci, Tendas, Dentamaro, Amadori, & Fabritiis, 2007). After conditioning, haematopoietic stem cells harvested from the patients themselves or an allogeneic donor prior to HSCT are infused to the patient to replace the ablated marrow. The patients then remain pancytopenic for around 14 to 21 days after stem cell infusion until engraftment occurs.
Although HSCT is potentially curative, various infective and non-infective complications may occur during the procedure. Among these complications, stomatitis is one of the commonest and most debilitating. It is defined as an inflammatory response characterized by the breakdown and ulceration of the mucosal lining of the oropharynx resulting from the effect of high-dose, myeloablative chemotherapy (Bhatt, Vendrell, Nau, Crumb, & Roy, 2010). It involves four phases including an inflammatory phase, an epithelial phase, an ulcerative phase, and a healing phase (Karthaus, Rosenthal, & Ganser, 1999). The first symptoms and signs of stomatitis including erythema and oedema of the soft palate, buccal cavity, tongue surface, and the floor of the mouth, appear approximately 7 to 10 days after administration of conditioning chemotherapy (Karthaus, Rosenthal, & Ganser, 1999). The non-keratinized parts, such as the buccal mucosa and tongue, are usually more severely affected, with the symptoms and signs persisting for up to 2 weeks, whereas the mean duration of symptoms and signs at the other sites of the oral cavity is around 6 days (Karthaus, Rosenthal, & Ganser, 1999).

Besides the severe pain experienced by the patients, stomatitis is also associated with other complications. Because of the pain, the patient’s oral intake is limited and usually requires parenteral nutrition. This may lead to cholestatic
jaundice and catheter-related infections (Niscola et al, 2007). Furthermore, due to
the mucosal breach, the patient is at increased risk of sepsicaemia and prolonged
antimicrobial treatment is often necessary. The use of antibacterial, antifungal, and
antiviral agents in this situation may cause various side effects including marrow
suppression, liver and renal function derangement, and allergic reactions (Niscola et
al, 2007). Occasionally, stomatitis may be so severe that the optimal dose of
chemotherapy could not be administered and the outcome may be adversely affected.
The overall results of these factors are a reduction in the patient’s quality of life, a
significantly prolonged hospital stay, and an escalation in the cost of care.

1.2 Affirming needs

Stomatitis significantly hampers the patients’ quality of life and increases their
complication rates during HSCT (Niscola et al, 2007). To most patients, the pain
associated with stomatitis is often considered to be the most debilitating part of
HSCT. It may be so severe that it could affect the quality of sleep, cause dysphagia,
and limit the patient’s ability to communicate with relatives and healthcare workers.
The lack of sleep adversely affects the patient’s emotional and physical conditions,
which are critical for successful treatment outcome. Dysphagia and reduced oral
intake lead to malnutrition and dehydration. Consequently, parenteral nutrition and
fluid replacement are required, and may lead to cholestatic hepatitis, fluid overload, and catheter-related infections (Niscola et al, 2007). Furthermore, dysphagia increases the risk of aspiration which can be life-threatening especially in immunocompromised patients undergoing HSCT (Niscola et al, 2007). These distresses are made worse because of the patient’s difficulty to communicate clearly with their relatives and the healthcare workers involved in their management.

Besides catheter-related infections and aspiration pneumonia, the impaired mucosal barrier also directly predisposes the patients to bacteraemia which is associated with significant morbidity and mortality. The risk of infection was found to be almost double in patients who developed mucositis during HSCT (Elting, Cooksley, Chambers, Cantor, Manzullo, & Rubenstein, 2003). This translates into an increase in the mean number of days with fever and the consumption of antimicrobial therapy. Furthermore, other supportive measures such as blood product transfusion and opiates infusion are often used to control the bleeding and pain of stomatitis. The use of these antimicrobial and adjunctive therapeutic agents is associated with undesirable side effects which may adversely affect the patient’s outcome. The direct effects and complications of stomatitis, as well as the additional treatment required for its management, result in an increase in healthcare costs and resource demand. It was reported that the hospital charges would be USD 43,000
higher for patients with stomatitis than those without for the period of hospitalization (Sonis, Oster, Fuchs, Bellm, Bradford, Edelsberg, Hayden, Eilers, Epstein, LeVeque, Miller, Peterson, Schubert, Spijkervet, & Horowitz, 2001).

Despite the devastating complications of stomatitis, evidence-based preventive interventions are lacking in current local setting, and the management approach mainly relies on symptomatic treatment and supportive care. The Multinational Association of Supportive Care in Cancer has established a guideline for the management of stomatitis and it emphasized that appropriate preventive measures may help to decrease the incidence and severity of stomatitis (Bhatt, Vendrell, Nau, Crumb, & Roy, 2010). In the HSCT centers in Hong Kong, a protocol of oral rinsing using normal saline, chlorhexidine, and caphasol during HSCT to maintain oral hygiene is employed currently. However, thanks to the high dose myeloblastic chemotherapy, satisfactory oral hygiene alone is not enough to prevent stomatitis. In contrast, a well-developed preventive protocol can help to minimize suffering of the patients and avoid prolonged hospitalization. At the same time, nurses who are involved in patient education, assessment, and coping with stomatitis, play an important role to bring these innovations into practice.

In some studies, oral cryotherapy has been advocated as an effective method for the prevention of stomatitis (Niscola et al., 2007). The proposed mechanism of action
is by local vasoconstriction which decreases blood flow to the oral mucosa. The impaired blood flow reduces the amount of cytotoxic drugs being distributed to the mucosal cells, and thus the damage of the mucosa, and the overall incidence and severity of stomatitis (Katranci, Ovayolu, Ovayolu, & Sevinc, 2011). It is not expensive and can be administered by the nurses easily. Nevertheless, conclusive high-level evidence of its efficacy and well-established protocols are not fully developed at present. Therefore, further clinical trials are urgently needed for this potentially useful, cost-effective, and relatively harmless intervention. The successful implementation of oral cryotherapy will be beneficial for the patients undergoing HSCT as it may hasten their recovery, shorten their hospital stay, and minimize their distressing experience and suffering.

1.3 Research question and Objectives

Research question

Is oral cryotherapy effective in reducing the incidence and severity of stomatitis in patients undergoing autologous HSCT?

Hypothesis

Oral cryotherapy is effective in reducing the incidence and severity of stomatitis in patients undergoing autologous HSCT.
**Objectives**

1. To review the existing literature and identify evidence of oral cryotherapy in the prevention of stomatitis for patients undergoing autologous HSCT.

2. To critically appraise and synthesize recommendations for the use of oral cryotherapy in patients undergoing autologous HSCT from the findings in the literature.

3. To apply the recommendations and establish an evidence-based protocol to reduce the incidence and severity of stomatitis in patients undergoing autologous HSCT.

4. To assess the potential for implementation of the protocol in the adult HSCT centers in Hong Kong.

5. To develop a plan for the implementation and evaluation of the protocol.
Chapter 2: Critical appraisal

2.1 Searching strategies

The relevant literature was searched in the electronic databases PubMed and ScienceDirect on 7th August, 2012, and in CLINAHL Plus (EBSCO HOST), ProQuest and Medline (OvisSP) on 5th and 10th September, 2012. The searching history is shown in Appendices 1 to 6.

Inclusion criteria

Study design

The searching process was limited to randomized controlled trials, clinical trials, cohorts and quasi-experimental studies conducted in English or Chinese.

Subjects

Patients at or above the age of 18 years with haematological malignancies who underwent autologous HSCT or those with other conditions who received high-dose chemotherapy regimens which were similar to the ones adopted in autologous HSCT were included. Both genders were included in the searching process.
Intervention

Oral cryotherapy including ice cube gargling and ice water rinsing were included in the search. The frequency and duration of the intervention was not limited.

Exclusion criteria

Articles belonging to the categories of letters to editor, editorials, case reports, and brief communications were excluded from the search. Patients who received chemotherapy which were markedly different from those used in autologous HSCT were excluded because the dose and degree of myelosuppression of these chemotherapy regimens were considered as major factors for the development of stomatitis in HSCT. Only chemotherapy regimens which were similar to those used in autologous HSCT were included.

2.2 Results

The literature search was conducted on 7th August, 5th September, and 10th September, 2012 in five databases including PubMed, ScienceDirect, CLINAHL Plus (EBSCO HOST), ProQuest, and Medline (Ovid SP).

Abstracts of 80 potential articles were screened. After assessing the articles with the inclusion and exclusion criteria and excluding the duplicated papers, five
eligible articles were selected for further quality assessment. Summary of the searching process was recorded in Appendices 1 to 6. The reference lists of the selected articles were screened for other relevant articles that were not included in the searching databases, and one additional suitable article was selected. Finally, five randomized control trials and one cohort study were selected.

Data from the six studies were extracted into Tables of Evidence as shown in Appendices 7 to 12. The quality of the literature was assessed with the help of the Scottish Intercollegiate Guidelines Network (SIGN) checklist (2011) (Appendix 19). The five identified randomized control trials were assessed with the checklist for randomized control trial whereas the cohort study was assessed with the checklist designed for cohort study.

2.3 Summary of the studies

Studies’ characteristics

The selected studies were published between 2004 and 2012. Five of them were randomized control trials and one was a cohort study. The studies were conducted in Turkey, Sweden, the United States of America, the Czech Republic, and Canada. The sample sizes ranged from 40 to 126.
Subjects’ characteristics

The subjects recruited in three of the studies were diagnosed with multiple myeloma (Lilleby et al, 2006; Salvador et al, 2012; Vanberg et al, 2007). Besides haematological malignancies, such as lymphoma, acute lymphocytic leukaemia, myeloma and acute myeloid leukaemia, two of the articles (Svanberg et al, 2007 & 2010) also included two subjects with testicular cancer. As they also received similar chemotherapy regimens as for autologous HSCT, these studies were included.

Similarly, in the study conducted by Karagozlu et al (2004), it was noted that patients were not diagnosed with haematological malignancies. The participants suffered from epidermoid cancer, small cell carcinoma, adenocarcinoma, and mesothelioma. The reason for including this study in the analysis was that the patients also received chemotherapy regimens (etoposide and platinol) which were similar to the ones adopted in autologous HSCT.

Age group

All the subjects in the six studies were reported to be older than 18 years. Five of them had reported the mean age of the subjects, which ranged from 49.8 years to 62 years. Neither the mean nor median age of the subjects was reported in the study by Karagozlu et al (2004), but it did report that 66.7% of the subjects were older than 60 years.
Gender

Around 70% of the subjects recruited in the studies by Karagoğlu et al (2004) and Lilleby et al (2006) were male, whereas the subjects recruited in the other studies had similar proportions of both genders.

The chemotherapy regimens adopted in the studies

The subjects in five of the studies received high-dose melphalan (200mg/m$^2$) for conditioning in HSCT (Lilleby et al, 2006; Salvador et al, 2012; Svanberg et al, 2007, Svanberg et al, 2010, Vokurka et al, 2011). Although two of the studies included patients who underwent both autologous and allogeneic HSCT, the data collected were analyzed separately so that comparisons of the differences in outcome between the two groups were available (Svanberg et al, 2007 & 2010).

Smoking / Drinking / Educational status

Not all of the studies reported the smoking, drinking and educational status of the subjects. Salvador et al (2012) reported that approximately 17% and 34% of the subjects in the study group were smokers and drinkers respectively, while the educational level was moderately average. Svanberg et al (2007 & 2010) reported that there was no significant difference in terms of tobacco use between two groups.
Baseline oral mucosal condition

Only two of the articles (Salvador et al, 2012; Vokurka et al, 2011) have reported the baseline oral mucosal condition of the subjects. Vokurka et al (2011) stated that the subjects did not have history of head and neck or total body irradiation. Salvador et al (2012) excluded patients who had head and neck irradiation which might increase the risk of stomatitis.

Intervention

All of the studies applied cryotherapy as a measure to keep the oral mucosa cool. However, the frequency and duration of cryotherapy in the studies were different. All of the studies administered cryotherapy by instructing the subjects to swirl the ice chips in the mouth, but the amount of ice chips being used varied among the studies.

Karagozolu et al (2004) instructed patients to move ice cubes in the mouth during chemotherapy administration. Lilleby et al (2006) arranged one ounce of ice chips for each subject and the process began 30 minutes before chemotherapy was started and lasted until 6 hours after the infusion of chemotherapy. The subjects rinsed their mouth every 30 minutes. Svanberg (2007 & 2010) instructed the subjects to suck on ice chips or rinse with cold water during chemotherapy
administration. Vokurka et al (2011) used ice lollipops, ice-cold water, or crushed ice for cryotherapy which started five minutes before and lasted until 15 minutes after chemotherapy administration. Salvador et al (2012) arranged two teaspoons of ice chips for each subject and the process started five minutes before, during, and after chemotherapy for a total of 60 minutes.

Control groups

Five of the studies adopted some measures in the control groups. Lilleby et al (2006) provided room temperature normal saline mouth rinsing for the control group. Whereas the remaining studies adopted a standard oral care including tooth brushing, mouth rinsing, application of moisturizer, dental treatment, provision of soft toothbrush and gentle toothpaste (Salvador et al, 2012; Svanberg et al, 2007, Svanberg et al, 2010, Vokurka et al, 2011). The study by Karagoğlu et al (2004) was the only one in which no oral care measure was arranged for the control group.

Assessment period

The measurement point and length of follow up varied among the studies. Four of the studies (Lilleby et al, 2006; Svanberg et al, 2007, Svanberg et al, 2010, Vokurka et al, 2011) carried out daily assessment from the day of chemotherapy
until 21 days after chemotherapy or until the subjects were discharged from hospital.

Karagozolu et al (2004) performed outcome assessment on day 1 and day 21 of chemotherapy for the subjects who received one day of chemotherapy, and assessed the outcome on day 1, 2, 3, and day 21 of chemotherapy for subjects who received three days of chemotherapy. Salvador et al (2012) performed assessment on day 3, 6, 9, and 12 of HSCT. The assessment in the follow-up period was based on the symptom trajectory of stomatitis.

Outcome measure

The studies mainly investigated the severity, pain level, and duration of stomatitis, and tolerability of cryotherapy. However, the measurement scales were not standardized among the studies. Some of them used justified grading scales for the severity of stomatitis measurement such as patient-judged mucositis grading, National Caner Institution (NCI) mucositis grading, the World Health Organization (WHO) mucositis grading scale, and oral mucositis assessment score (OMAS).

(1) Incidence of stomatitis

The incidence of stomatitis was measured in one of the studies (Vokurka et al, 2011). It was reported that the incidence was statistically significantly reduced in
the study group as compared with the control group (22% vs. 78%; p <= 0.0001).

(2) Severity of stomatitis

The severity of stomatitis was assessed in all of the six studies, it was commonly concluded that only a small percentage of subjects in the study groups developed severe stomatitis and the results were statistically significant among the studies.

(3) Pain level experienced

Lilleby et al (2006) and Salvador et al (2012) investigated the pain level experienced by the participants. Both studies reported a lower pain level in the study group than in the control group (mean score: 0.41 vs. 1.06; 0.3 vs. 1.64 reported in the two studies respectively).

(4) Days and dose of narcotics used for stomatitis

Lilleby et al (2006) reported fewer days of intravenous narcotics being used in the study group than in the control group (0 vs. 5.5 days; p = 0.0003). Salvador et al (2012) and Svanberg et al (2007) also stated that smaller amounts, fewer days and dose of opioids were administered in the study groups.
(5) **Duration of stomatitis**

Two of the studies reported on the duration of stomatitis and number of days with grade 3 stomatitis (Karagoğlu et al, 2004; Lilleby et al, 2006).

**Conclusion**

All of the identified studies concluded that cryotherapy was effective in preventing severe stomatitis. Only one of the studies (Vokurka et al, 2011) specifically showed a reduction in the incidence of stomatitis. Three of the studies (Karagoğlu et al, 2004; Lilleby et al, 2006; Vokurka et al, 2011) reported that a shorter duration of severe stomatitis was experienced by the study group. In addition, Lilleby et al (2006), Svanberg et al (2007) and Salvador et al (2012) reported that lower pain scores as well as number of days of using intravenous narcotics were observed in the study group. Salvador et al (2012) and Vokurka et al (2011) also investigated the tolerability of cryotherapy which was reported to be well tolerated.

**2.4 Quality assessment strategy**

The qualities of the articles were assessed based on the SIGN framework. The details of the appraisal are presented in Appendices 13 to 18. The SIGN checklists for randomized control trial and for cohort study were employed for the assessment.
of the five randomized control trials (Karagoğlu et al, 2004; Lilleby et al, 2006; Svanberg et al, 2007; Svanberg et al, 2010 & Salvador et al, 2012) and one cohort study (Vokurka et al, 2011) respectively.

2.4.1 Quality assessment of the five randomized control trials

For the five randomized control trials (Karagoğlu et al, 2004; Lilleby et al, 2006; Svanberg et al, 2007; Svanberg et al, 2010 & Salvador et al, 2012), the SIGN checklist for randomized control trial was used to assess the quality. The details of the checklist are presented in Appendices 13 to 17.

Randomization

The research questions in all five studies were appropriate, clearly focused, and well covered. The assignments of the subjects to treatment groups were randomized in all five studies. Specifically, the studies conducted by Salvador et al (2012) and Svanberg et al (2010) have detailedly reported on the randomization method of the assignment of the subjects which minimized allocation bias during the process, lowered the confounding effect in the studies, and increased the validity of the results.

The concealment method was not reported in most of the selected studies. Only
Salvador et al (2012) has mentioned the concealment method with the use of sealed envelopes. Furthermore, only Salvador et al (2012) has specifically mentioned on the research assistant who assessed the patients being blinded from the intervention. Blinding, especially double-blinding, could minimize bias in the study because the intervention effect would be otherwise affected by the subjects if they knew which group they were allocated to. However, blinding of the subjects seemed to be difficult as most of the studies implemented the intervention with active involvement of the subjects who knew which group they were allocated to. Blinding of the nurses was also difficult as they needed to carry out the daily nursing care including assessment and management of the related complications.

**Subjects**

Almost all of the studies recruited subjects with an equal proportion of gender and age between the control and treatment groups except for the study conducted by Lilleby et al (2006) in which a larger proportion of subjects were male in both the control and treatment groups. All of the studies except the one conducted by Karagoğlu et al (2004), as stated before, involved subjects who suffered from haematological malignancies and underwent HSCT.
All five studies have adequately addressed the subject characteristics such as age and gender. Some of them have also reported the subjects’ body mass index (BMI) (Vokurka et al, 2011), basal oral mucosal condition, smoking and drinking status (Svanberg et al, 2010) so as to provide a detailed and clear background of the subjects.

**Outcome measure justification**

Outcome measures were documented in a clear manner in the studies. However, since there was no standardized measurement scale for the assessment of stomatitis, the comparison between the different studies was difficult. In practice, the WHO oral grading score and the National Cancer Institute Common Toxicity Criteria (NCI-CTC) for oral mucositis are commonly used for the assessment (Naidu, Ramana, Rani, Mohan, Suman, & Roy, 2004). In addition, the Oral Mucositis Assessment Scale (OMAS) also demonstrated high clinical correlation and allowed an accurate response to stomatitis. Most of the identified studies adopted the measurement scale from the WHO, NCI-CTC and OMAS. In addition, they provided justification and clear explanation for the outcome measures they adopted.
**Drop-out rate**

The drop-out rate ranged from 2.17% to 3.75% among the studies. One of the studies (Karagozlu et al, 2004) did not mention the drop-out rate. The rate was considered to be reasonable. Only two of the studies (Svanberg et al, 2007 & Svanberg et al, 2010) have used the intention-to-treat analysis. By analyzing the result based on the preliminary intervention assignment, it avoided bias generated by the drop out of subjects.

**2.4.2 Quality assessment of the cohort study**

For the cohort study (Vokurka et al, 2011), the SIGN checklist for cohort study was used to assess the quality. The details of the checklist are presented in Appendix 18.

The study addressed the question and the subject characteristics in a clear and appropriate way. The study recruited 128 subjects from multiple centers. They were diagnosed with haematological malignancies and received chemotherapy for autologous HSCT. However, it did not mention the number of subjects who were selected from the total population and the comparison between the subjects who attended the full follow-up and those were lost to follow-up. Potential confounders such as diabetes mellitus, removable dentures, number of days since last
chemotherapy, history of stomatitis, and baseline oral condition were assessed for their roles in causing stomatitis. The WHO grading system of stomatitis was adopted and the outcome measure was adequately addressed and justified. The confidence intervals were provided. The drop-out rate was low and no blinding was used in the study. The confounders were identified by the researcher and taken into further analyses in order to minimize bias and examine the risk factors for stomatitis.

2.5 Data synthesis

Summary of the diversity of conclusions

Despite the differences in the study design and the level of evidence among the selected studies, they all concluded that the effects of cryotherapy on the prevention of stomatitis and reduction in severity were strong. Nevertheless, the efficacy of cryotherapy demonstrated between studies varied to a certain extent because of the presence of intrinsic and extrinsic factors.

Intrinsic factors

There was no standardized assessment scale for stomatitis adopted in the selected studies. Hence, the oral conditions were measured and reported with different scales, which made direct comparison of efficacy difficult. In addition, the duration of cryotherapy applied to the treatment groups had an important implication.
to the result. Furthermore, some studies also implemented oral care protocols for the
control group, which might result in positive effects on stomatitis prevention and
severity reduction.

Extrinsic factors

Most of the studies did not report the body mass index, baseline of oral
conditions, and the amount of chemotherapy administered prior to the study, which
were potential variables of developing stomatitis (Raber-Durlacher, Barasch,
Peterson, Lalla, Schubert, Fibbe1, 2004). The chemotherapy regimens used in the
studies included high-dose melphalan, vepesid, cisplatin and BEAM (carmustine,
etoposide, cytarabine, arabinoside and melphalan) (Karago¨ zog˘ lu et al, 2004;
Svanberg et al, 2007; Svanberg et al, 2010) for patients with different underlying
conditions, and different regimens might affect the development and severity of
stomatitis. According to Stiff (2001), high-dose melphalan and etoposide were the
most likely agents to cause severe mucositis.

The subjects’ adherence to the intervention played an important role in the
reliability of the results. While some studies reported good adherence among the
subjects, the study by Lilleby et al reported that compliance was not universal
among the subjects and some data were missing. The interpretation of the results
could be altered in the absence of those missing data.

**Conclusion**

Stomatitis is a serious and challenging complication in patients who undergo autologous HSCT. While the traditional management approach for stomatitis is mainly symptomatic and supportive, significant emotional and physical distress is often observed. With the help of a well-designed, evidence-based guideline on stomatitis prevention and severity reduction, it is anticipated that patients’ suffering can be minimized and their qualities of life during HSCT can be greatly improved. The findings in the literature strongly supported the use of cryotherapy as an effective prophylactic measure for stomatitis in these patients, with an overall decrease in duration and severity of stomatitis being clearly demonstrated. The development of a definitive evidence-based protocol for the use of cryotherapy is urgently needed and should be adopted in HSCT centers in order to enhance the overall quality of patient-centered care.
Chapter 3: Implementation Potential

The implementation of ice water mouthwash to prevent stomatitis in patients undergoing autologous haematopoietic stem cell transplantation (HSCT) is supported by research findings. Before putting the proposed evidence-based protocol into practice, the implementation potential should be assessed thoroughly. In this chapter, the target setting, target population, transferability, feasibility and cost-and-benefit ratio of the proposed intervention protocol will be discussed in order to examine the appropriateness of applying the protocol in the target health care setting.

3.1 Target setting / Population

Target setting

The intervention protocol will be implemented in the adult HSCT center at the Department of Medicine in the university-affiliated Queen Mary Hospital in Hong Kong. The center is a high dependency unit with 10 isolation rooms and serves both male and female patients. Each isolation room has one bed and is secured with double doors with positive pressure airflow and high-efficiency particulate air (HEPA) filter for the protection of the extremely immunocompromised patients undergoing HSCT. Patients with haematological malignancies requiring HSCT will
be admitted to the center and stay in the individual isolation rooms during the conditioning phase, marrow-infusion phase, the pre-engraftment phase, and the post-engraftment phase for an average of 30-50 days. The proposed protocol will be implemented by the nurses who work in the HSCT center. At present, there are fourteen Registered Nurses (RN) including three Advanced Practice Nurses (APN) and a Specialty Nurse (NS) working in the center.

**Target population**

The target audience includes patients who are:

- Aged 18 years or above;
- Male or female;
- Diagnosed with haematological malignancy;
- Admitted for autologous HSCT in the adult HSCT center;

**3.2 Transferability of the findings**

Regarding the transferability of the research findings into local practice, the following aspects are discussed: similarity of the target setting and population, philosophy of care, number of clients benefiting, and time frame for implementation and evaluation.
3.2.1 Target Setting and Population

All reviewed studies were conducted in an inpatient setting. However, specific isolation setting was not mentioned in the studies.

Excluding two studies (Svanberg et al, 2007; Svanberg et al, 2010) which have included two subjects diagnosed with testicular cancer; all subjects recruited in the reviewed studies were diagnosed with haematological malignancies. The subjects’ characteristics in the studies as discussed in the previous sections were comparable with the target population in terms of age, gender, diagnosis and chemotherapy regimen received. In Hong Kong, around 41.8% of the patients who undergo HSCT are aged >40 years and slightly more patients are male (Lie, Au, & Liang, 2009). The most common indications for transplantation are acute myeloid leukaemia, chronic myeloid leukaemia, lymphoma, acute lymphoblastic leukaemia and myeloma (Lie, Au, & Liang, 2009). These background demographic characteristics are similar to those described in the reviewed studies.

3.2.2 Philosophy of care

The core value of the Hospital Authority is to always provide high quality patient-centered care as the top priority. The Hospital Authority aims to improve clinical practice through implementing continuous quality treatment strategies which
have been proved to be improving clinical outcomes and service efficiency in a cost–effective way (HA Strategic Service Plan, 2012).

In addition, as stated in the Hospital Mission Statement (2012), the Hospital Authority encourages measures which can promote staff’s motivation to provide high quality patient-centered service in an effective manner. In view of the Hospital Mission Statement, nurses undoubtedly have an essential role and responsibility to provide the most optimal intervention so as to promote patients’ well-being and minimize their suffering. The underlying philosophy of care and core value of the evidence-based protocol described in the current study concurs with that of the Hospital Authority, and trying to minimize patients’ suffering and restoring their quality of life.

3.2.3 Number of people benefiting

Effective resource distribution is important in any service plan development. In order to ensure that the resources are allocated effectively, the proposed protocol must be beneficial to a significant number of people.

This proposed protocol is beneficial to all adult patients undergoing autologous HSCT. According to the statistics in the target setting, there were around 100 cases of autologous HSCT performed in the center every year.
3.2.4 Time frame

The proposed protocol can be implemented in the center after a two-month consultation phase of comprehensive discussions with relevant parties including the ward manager, haematologists, nurse specialists, advance practice nurses and registered nurses in the ward. In addition, the benefits, potential risks and resource needs for the protocol will be discussed with the relevant parties during the consultations. After the consultation phase, training sessions will be provided to the registered nurses in the preparation phase lasting for one month. The protocol and the evaluation method will be explained to the nurses. The resource needs will be addressed and obtained with the assistance of the ward manager.

After the consultation and preparation phases, the proposed protocol will be implemented as a pilot trial in the center for the initial three months. Data of the progress and outcome, and feedbacks from staff and patients will be analyzed and reported to the ward manager, haematologists and nurse specialists for further optimization of the protocol. The optimized protocol will then be implemented in the center for another six months and evaluation will be conducted at the end.
3.3 Feasibility

To assess the feasibility of the proposed protocol, the availability of the manpower, resources and skills required for the protocol implementation were investigated.

3.3.1 Organizational climate

A supportive organizational climate certainly facilitates the implementation of the new protocol. In Queen Mary Hospital which is a university-based teaching hospital, there is an encouraging atmosphere for conducting clinical researches and implementing evidence-based interventions. In the haematology team, a highly educational journal club is organized every week. The ward manager, physicians and nurses of the haematology team are encouraged to share their most updated literature reviews in the journal club. Opinions which can improve clinical practice are welcomed. In addition, nurses are encouraged and have the autonomy to initiate interventions to patients. For example, the current mouth washing protocol was initiated and developed by nurses in the HSCT center years ago after thorough discussion in the journal club.
3.3.2 Support from administration and frontline staff

Besides the supportive stand of the hospital, support from administration and frontline staff is also an essential element in ensuring the efficient implementation of the protocol. Before the initiation of implementation, the protocol should first be approved by the Department Operation Manager, ward manager, haematologists–in-charge and nurse specialists. To gain support from the frontline staff, a clearly stated aim and an easily comprehensible protocol are essential. The engagement of nurses in active participation in the development of the evidence-based protocol can promote a stronger sense of autonomy and confidence, and at the same time improve the patients' quality of life. Consequently, nurses will become convinced of the benefits of evidence-based interventions which can promote patients’ health outcome.

3.3.3 Potential barriers

All potential barriers of the protocol implementation shall be taken into consideration. Firstly, the proposed protocol has to be approved by the Department Operation Manager and ward manager, as well as the physicians-in-charge. Effectiveness of the intervention, potential benefits and risks to patients are their major concerns for the protocol. Therefore, the protocol’s strong evidence-based
background and potentially large cost-to-beneficial ratio with minimal risk to patients should be presented to them in detail.

Secondly, support from frontline staff can be the second potential barrier as their routine nursing care will face some changes especially because not much additional manpower and resources may be available for the implementation of the protocol. Extra time and nursing skills are needed for the new knowledge of protocol implementation. However, the frontline staff’s concerns about the disruption of routine care can be minimized with a simple and clearly written protocol. In addition, their opinions of the protocol will be collected and analyzed before and after implementation. Improving patients’ health outcome, fostering their recovery rate and reducing their rate of complications can certainly reduce the needs of further intensive nursing care which is also beneficial to the frontline staff.

3.3.4 Potential interference of staff routine practice

In current practice, nurses perform basic oral assessment for the patient with the use of the Oral Assessment Guide (OAG) on the day of admission. The oral assessment is conducted every morning until the patient is discharged. Normal saline, chlorohexidine and caphasol are provided to the patients for mouth washing before and after meals during hospitalization. Supportive measures such as morphine and
total parental nutrition infusion are provided to patients for pain control. The proposed protocol aims to improve on the existing practice by using ice water for mouth washing during the administration of chemotherapy so as to minimize the amount of cytotoxic drugs distributed to the oral mucosal layer hence reducing the rate of severe oral stomatitis. Therefore, in addition to the daily nursing assessment of oral condition, nurses have to assess whether the patients are suitable for the proposed protocol such as their tolerability to cold water, provide them with appropriate equipments, as well as document their oral condition after receiving the intervention. Furthermore, the nurses need to learn and adapt to the WHO grading (Appendix 20) used in the proposed protocol for the assessment of the oral condition assessment in the proposed protocol.

3.3.5 Skill requirement for nursing staff

Although the protocol and assessment tool are new to the staff, the nurses currently working in the HSCT center already possess skills for oral assessment. Training will be provided to nurses for the initiation of the intervention, pre- and post-intervention oral assessment methods, management of adverse effects such as the sensitivity and discomfort of patients’ teeth to ice water, and the indications for terminating the intervention. Pamphlets with details of the intervention and the
evaluation methods will be provided to them. They will be encouraged to attend a thirty-minute training session to have a more comprehensive understanding of the proposed protocol.

3.3.6 Availabilities of equipment and measuring tools

Equipments like cups, ice maker, and boiled water are already available in the HSCT center. Nevertheless, the new assessment tool (WHO Oral Mucositis Grading Scale) has to be prepared for the protocol implementation. Besides documentation forms, no extra equipment is needed for this protocol.

3.4 Cost – Benefit ratio of the proposed protocol

3.4.1 Potential risks

The major potential risk of this protocol is coldness-related intolerance. Patients may have sensitive teeth to coldness and may experience a sharp uncomfortable sensation which is difficult to tolerate. This potential problem is reported in two of the reviewed articles. However, this problem can be resolved when the cooling sensation subsides spontaneously after the ice water is removed. Another potential risk occurs when patients accidentally swallow the cold gargling water. Therefore, only boiled water will be used for making ice cube so as to avoid
them from swallowing cold tap water in accident in order to minimize the risk of infection.

3.4.2 Potential benefits to patients

The proposed protocol has numerous potential benefits to patients. These include the reduction of risk of developing severe oral stomatitis, loss of nutritional balance, systemic infection, need of morphine infusion, and prolonged hospitalization period. These potential benefits are critical to the improvement of the overall quality of life of the patients and thus make this minimally invasive protocol desirable.

3.4.3 Potential benefits to nurses

The protocol also creates potential benefits to nurses. On one hand, it strengthens the nurses’ interest towards exploring evidence-based interventions and the possibility of implementing a new protocol in clinical setting. In addition, this helps them to develop autonomy as well as job satisfaction by participating in developing and improving nursing care protocol.

On the other hand, reducing patients’ risk of complications can certainly reduce the workload of nurses. Less time and effort is needed to take care of patients who
do not develop severe oral stomatitis and its related complications.

3.4.4 Potential benefits to the Hospital

From the hospital’s perspective, the proposed protocol can reduce expenditures on use of antibiotics, pain killer, total parental nutrition infusion, and prolonged hospitalization. In addition, shortening patients’ length of stay can shorten the long queue of the HSCT hence providing service to more patients in need.

3.4.5 Cost for implementation of proposed protocol -- Material costs

Since most of the equipments needed are available in the exiting setting, the material cost for implementation of the proposed protocol is minimal. The costs of establishing the protocol for 10 patients in 3 months is around HKD 3200. It includes material purchase as well as nurses training. Details of the material costs are shown in Appendix 21. Extra cost will be spent for using boiled water or normal saline for making ice cubes as patients may accidentally swallow the cold water. Therefore, only boiled water or normal saline should be used for making ice cube and the gargling so as to avoid them from swallowing cold tap water in accident. This would minimize the risk of infections.
3.4.6 Cost for implementation of proposed protocol -- Non-material costs

Extra non-material costs required is limited for the implementation of the proposed protocol. No extra staff is expected. The nurses already possess the skills and equipments for oral assessment. The only additional human resources needed are the pre-implementation training sessions, the time needed to monitor the tolerability of patients to ice water gargling, and the collection of opinions from patients.

3.4.7 Costs for maintaining current practice

The costs of taking care of patients with severe oral stomatitis including for hospitalization, antibiotics, medications as well as total parental nutrition commonly used in the hospital are shown in Appendix 22. The total cost is huge even if treatment is provided for only 15 patients suffering from severe oral stomatitis for one week. Moreover, extra time is needed for the complicated nursing care, blood product transfusion as well as emotional support for the patients. Compared with the costs for maintaining current practice, the extra cost needed for the implementation of the protocol is minimal. Furthermore, the cost of putting patients at risk of undesirable pain and septicemia is unaffordable for health care practitioners.
3.4.8 Conclusion

The proposed protocol is transferable and feasible for the target settings and audiences. It is appreciably beneficial to patients, staff, as well as the institution. Although there are potential barriers for the implementation of the protocol, a favorable cost-to-benefit ratio can strengthen the viability of the proposed protocol in clinical setting. In addition, good communication skills as well as a clearly written protocol are definitely critical for smooth protocol implementation in the different phases.
Chapter 4: Developing Evidence-Based Practice Protocol

After discussing the transferability, feasibility and the cost-benefit ratio of the proposed protocol, an evidence-based protocol is developed in this section.

Title of the guideline

“Evidence-Based Intervention Protocol of Using Ice Water Mouthwash in the Prevention of Stomatitis for Patients Undergoing Autologous Haematological Stem Cell Transplantation”

4.1 Objectives

The objectives of this evidence-based protocol are:

1) To reduce the rate of developing severe oral stomatitis for patients who undergo autologous HSCT due to administration of high-dose myeloblastive chemotherapy.

2) To standardize nursing care provided to patients for the reduction of severe stomatitis development.

3) To reduce oral stomatitis related medical costs and complications.
4.2 Target population

The target population of this protocol is the adult patients diagnosed with haematological malignancies who are admitted to the adult HSCT center at Queen Mary Hospital for autologous HSCT.

4.3 Rating scheme of the protocol

The recommendations of this clinical protocol are graded according to the Scottish Intercollegiate Guidelines Network (SIGN) (2011) which rates the recommendations according to the strength of evidence. The grades of recommendations are graded with A – D; whereas strength of evidence of the reviewed studies is rated with 1++ to 4. The rating scheme is shown in Appendix 19.

4.4 Recommendations

Recommendation 1

- The ice water mouth wash intervention is applicable to adult patients who are undergoing autologous HSCT.

Grade of Recommendation: A

Evidence Discussion:

The age range of the subjects in the reviewed studies was quite large. Although
older patients might be at higher risk of developing stomatitis (Raber-Durlacher et al, 2004), subjects with a median age of 50 years have demonstrated satisfactory response to stomatitis prevention and severity reduction (Karagozolu et al, 2004 [level of evidence 1+]; Lilleby et al, 2006 [level of evidence 1-]; Salvador et al, 2012 [level of evidence 1++] ; Svanberg et al, 2007 [level of evidence 1+] ; Svanberg et al, 2010 [level of evidence 1+]; Vokurka et al, 2011 [level of evidence 2+]). Since no specific age range was reported to be unsuitable for the intervention, the proposed guideline is applicable to all adult participants.

In most of the reviewed studies, ice water gargling was applied to patients undergoing autologous HSCT and reported to have statistically significant reduction in the severity of stomatitis (Lilleby et al, 2006 [level of evidence 1-]; Salvador et al, 2012 [level of evidence 1++]; Svanberg et al, 2007 [level of evidence 1+]; Svanberg et al, 2010 [level of evidence 1+]; Vokurka et al, 2011 [level of evidence 2+]).

Therefore, the proposed guideline shall target all adult patients who are diagnosed with haematological malignancies and undergoing autologous HSCT.
**Recommendation 2**

- Ice water mouthwash should be provided to patients and supplementary ice chips should be provided during intravenous chemotherapy administration to keep their oral cavity cool.

**Grade of Recommendation: A**

**Evidence Discussion:**

The method of administering cryotherapy differed among the studies, but most of them reported the use of crushed ice chips for rinsing and gargling. The amount of ice chips was not mentioned except in the studies by Salvador et al (2012) [level of evidence 1++] which stated that two teaspoons of ice chips were used and the subjects continued the ice chips gargling until the ice chips melted, and Lilleby et al (2006) [level of evidence 1-], which reported the use of one ounce of ice chips for oral rinsing. It was concluded that the amount of ice chips used in the proposed guideline should not be limited in order to keep the subjects’ oral cavity cool.

**Recommendation 3**

- The ice water mouthwash should be initiated five minutes before chemotherapy infusion and stopped 30 minutes after the infusion.

**Grade of Recommendation: A**
Evidence Discussion:

All the studies stated that the cryotherapy started five minutes before chemotherapy infusion (Karagozoglu et al, 2004 [level of evidence 1+]; Lilleby et al, 2006 [level of evidence 1-]; Salvador et al, 2012 [level of evidence 1++]; Svanberg et al, 2007 [level of evidence 1+]; Svanberg et al, 2010 [level of evidence 1+]; Vokurka et al, 2011 [level of evidence 2+]). The cessation of cryotherapy ranged from immediately after chemotherapy infusion was finished (Karagozoglu et al, 2004) [level of evidence 1+] to six hours after infusion (Lilleby et al, 2006) [level of evidence 1-]. Despite the differences in the duration of intervention, satisfactory results were reported. Considering the patients' tolerability, 30 minutes of ice water gargling would be sensible and practical.

Recommendation 4

- For chemotherapy which was administered for more than one day, ice water gargling should be performed during each course of chemotherapy.

Grade of Recommendation: B

Evidence Discussion:

According to Niscola et al (2007), the risk of oral ulcer increased with each course of chemotherapy when multiple courses were given. Therefore, as stated by
Karagozlu et al (2004) [level of evidence 1+], cryotherapy should be implemented in all courses of chemotherapy instead of just the first day.

**Recommendation 5**

- The daily assessment of oral condition should be carried out daily from the day of chemotherapy until 21 days of HSCT for the protocol.

**Grade of Recommendation: A**

**Evidence Discussion:**

The assessment of patients’ oral condition lasted for 12 - 21 days in five of the reviewed studies which covered the whole neutropenic pre-engraftment phase that patients would experience after receiving myeloablative chemotherapy. Patients undergoing autologous HSCT are susceptible to severe stomatitis during this neutropenic pre-engraftment phase (Niscola et al, 2007). (Karagozlu et al, 2004 [level of evidence 1+]; Lilleby et al, 2006 [level of evidence 1-]; Svanberg et al, 2007 [level of evidence 1+]; Svanberg et al, 2010 [level of evidence 1+]; Vokurka et al, 2011 [level of evidence 2+]).
Recommendation 6

- The intervention should be stopped if the patient reported intolerability to ice water or sensitive teeth to coldness.

Grade of Recommendation: B

Evidence Discussion:

The major potential risk of this protocol is the coldness-related intolerance. Patients have teeth sensitive to cold may experience a sharp cooling sensation and find the cooling sensation intolerable. This potential problem is reported in two of the reviewed articles (Lilleby et al, 2006 [level of evidence 1-]; Salvador et al, 2012 [level of evidence 1++]). This problem can be resolved when the cooling sensation subsided spontaneously after removal of the ice water.

Recommendation 7

- The WHO grading as well as visual analog scale will be adopted as the assessment tool in the protocol.

Grade of Recommendation: A

Evidence Discussion:

A standardized and accurate assessment tool is a critical component in a well developed guideline. Both the WHO and NCI grading are well justified and highly
recommended for oral assessment (Cella, Pulliam, Fuchs, Miller, Hurd, Wingard, Sonis, Martin, & Giles, 2003). As suggested by Vokurka et al (2011) [level of evidence 2+], the assessment of stomatitis should not be limited to objective biological data only, but should also include the subjects’ subjective feelings. The WHO grading includes the objective, subjective, as well as functional aspects of mucositis, and is therefore an appropriate assessment method in the proposed guideline. According to Salvador (2012) [level of evidence 1++], the WHO grading scale is widely used in both medical and nursing researches and it is commonly used as a general comparison index.

Since pain was often considered as the most distressing element of stomatitis, pain score should also be included as an outcome measure. As stated by Harris and Knobf (2004), visual analog scale was commonly used for pain intensity assessment. This numeric scale was widely used and demonstrated to be reliable and valid. It is adopted in four of the reviewed studies (Lilleby et al, 2006 [level of evidence 1-] ; Salvador et al, 2012 [level of evidence 1++] ; Svanberg et al, 2007 [level of evidence 1+] ; Vokurka et al, 2011 [level of evidence 2+]).
Evidence-based clinical protocol on ice water mouthwash to prevent stomatitis in patients undergoing autologous haematopoietic stem cell transplantation (HSCT) was discussed in the previous chapter. Before implementing a new protocol to a clinical setting, an implementation plan will be established in order to communicate with all relevant stakeholders. This can gain support from the stakeholders so as to facilitate the protocol implementation.

5.1 Communication Plan

5.1.1 Identification of Stakeholders

Stakeholders are anyone that will affect or be affected by the proposed change (Rebecca, 2011). Comprehensive identification and consideration of stakeholders’ concerns is essential to the successful implementation of a new protocol. The key stakeholders of proposed protocol are the in-charge persons of the medical and nursing team in the HSCT center, including the Ward Manager (WM), Department Operative Manager (DOM) and Chief of Service (COS). They have the authority to approve the protocol implementation and resources allocation.

The other stakeholders include the haematology consultants and medical officers
who are responsible for daily HSCT patients’ medical management. They will be taking care of HSCT patients with new protocol implementing on them.

The Advance Practicing Nurses (APN), Nursing Officers (NO) and Nurse Specialist (NS) working in HSCT center are another key stakeholders because they are responsible for supervising the standard of nursing care. Their advices on making the protocol feasible and practicable in the center are essential. In addition, the frontline nurses who are responsible for executing the new protocol are inevitably becoming the key stakeholders. They will assess patients’ oral condition everyday and possess the autonomy to offer the interventions to them based on patients’ oral condition. They all have experiences and skills to handle the potential problems furthermore they can provide advices for the modifications for the protocol when necessary.

5.1.2 Communication Plan with Administrators

The communication plan will start with informal discussion of the existing problems with senior frontline nurses. As they are experienced in providing nursing care for HSCT patients, their opinions towards the proposed protocol are productive. Their comments will be collected for preliminary protocol amendment. Some frontline staff may oppose the new protocol due to the fear of increasing daily
workload. A small meeting will be held for them to express their concerns and evidence from the reviewed studies will be provided that maintaining the current practice may increase workload due to the increase in complications, and explaining to them that no additional skill is required for the proposed protocol.

With general consensus among the frontline staff, the proposed protocol will be presented to the NS, APN and NO introducing the aims, problems of current practice, significance as well as urgency of this proposed protocol. Table of evidence of the reviewed articles will be illustrated to explain that the protocol is strongly evidence based and how was the content of the protocol set up according to the strength of evidence. The inclusion and exclusion criteria, timeframe of the trial, resources needed, possible resistance and solutions, cost-benefit ratio of the protocol, and outcome measures of the program will be explained together with a comprehensive report. Being the clinical advisors of the center, they will give clinical advice and supervision to subordinate nurse colleagues in daily practice. Their constructive advices can surely streamline and propagate the protocol with other administrators and assist other nursing colleagues to carry out the protocol. After the refinement of the protocol, a detail proposal will be introduced to the ward manager (WM) for her approval. Implementation potential analysis including significance as well as urgency of this proposed protocol, transferability, feasibility, cost-benefit ratio as well as the
resources needed will be explained.

With the approval of clinical advisors, a formal proposal will be presented to the Chief of Service (COS) and the Department Operation Manager (DOM) in a meeting chaired by the WM, APN, NO and the NS. A thirty minutes presentation covering all important information of the proposed protocol will be delivered to them with a printed outline. Support and approval from COS and DOM will be mostly appreciated as they are the one who has the authority to approve the protocol implementation and resources allocation.

5.1.3 Communication with Haematology Doctors

Haematology consultants and medical officers are the key stakeholders in this proposed protocol as they are responsible for daily HSCT patients’ medical management. And they will make decision if it is appropriate to adopt the new protocol on HSCT patients to prevent oral stomatitis. They will be invited to attend a one-hour meeting with WM and NS explaining the aim, significance and the feasibility of this protocol after the approval of COS and DOM. Their opinions and support for this protocol will be highly appreciated and amendments shall be made according to their medical considerations.
5.1.4 Setting up a Steering Committee

After obtaining the approval from the administrators, a Steering Committee will be formed. The Committee will include one NS, one doctor, three frontline nurses and the proposer will act as the coordinator in the Committee. The members of the Committee will attend a one-hour training session which is held by the proposer explaining the content of protocol and the implementation method. The Committee is responsible for six main aspects in this proposal: (1) Maintain communication between different stakeholders. (2) Monitor and facilitate the protocol implementation. (3) Provide assistance to frontline staff when they have enquires. (4) Collect opinions from stakeholders including frontline staff and patients. (5) Promote the new protocol to other staff in HSCT center. (6) Take part in training and evaluation of the pilot trial and make recommendations for the protocol.

The Committee meeting will be held every month for first half year then every two months. WM will be invited to join the committee meeting in order to understand the progress of the implementation and provide support and advices if necessary.

5.1.5 Communication with Nurses

The new protocol will be promoted to the staff in the weekly ward meetings, in which inadequacy of the existing practice, aim of the protocol and also the content of
the protocol will be highlighted in the meeting. A clearly written protocol will be distributed to the staff and posters will be placed on the notice board to increase staff awareness, and copies of the protocol together with the reference journals of the protocol will be available in ward areas. Frontline staff will be encouraged to express their opinions and concerns to the steering committee as well as the proposer.

The new protocol will commence with providing one hour training to the frontline staff. Compensation hours will be granted to nurses if they attend training session after duty with the approval of WM and DOM so as to enhance their compliance. The training session will be held by the proposer and three frontline nurses in the steering committee and they will act as role model in the center. The new protocol, assessment tools, intervention, documentation as well as data collection method will be introduced. Staff will be required to fill in a post-test questionnaire to ensure they are competent in carrying out the protocol. During the implementation of the protocol, they are welcomed to consult the steering committee members or the proposer.

5.1.6 Sustaining the Change

Once the change is initiated, proposer and the steering committee shall put their focus on how to sustain the change. Nurses’ adherence to the new protocol will be
monitored by auditing their charting and documentation. Equipment and resources needed should be always available to the staff. Comments and feedbacks from nurses will be collected and discussed during the weekly ward meeting throughout the implementation period. During the monthly steering committee meeting, difficulties encountered, patients’ outcome towards the intervention will be discussed and modifications of the protocol will be made accordingly and will be announced to the frontline staff during daily handover time.
Chapter 6: Pilot Testing Plan

A pilot test will be conducted to test the feasibility of the guideline. It is a trial run which can test the logistics of the guideline before a large scale implementation (Rebecca, 2011). In addition, this will determine whether any revision of the protocol is needed before implementing the protocol in a larger scale. Therefore, a pilot test will be carried out in the HSCT center for three months in advance.

6.1 Objectives of the Pilot Testing Plan

The objectives of the pilot testing plan are:

1. To examine the feasibility of the protocol

2. To identify any logistic or technical problems occurring during the implementation of the protocol

6.2 Study Design and Sample Recruitment

The pilot test will last for three months and will be performed in the HSCT center. From the previous admission record in the ward, there will be around twenty eligible patients being recruited in the pilot test on admission to the HSCT center by
nurses. Therefore, the sample size of the pilot test is expected to be twenty. The inclusion and exclusion criteria of the samples in this pilot test are identical with the actual recruitment criteria in the proposed guideline. Written consent will be obtained if they agree to join the pilot test.

6.3 Data Collection and Analysis

Baseline assessment

After patient recruitment, the nurses will explain the detailed information of the intervention to the patients with the use of a pre-designed leaflet. The nurses will assess and document the patients’ baseline characteristics including age, gender, smoking status, BMI, and oral condition.

Intervention

Ice water gargling will be offered to the patients according to the proposed protocol once chemotherapy is started and their oral conditions will be assessed by the nurses everyday. The WHO Oral Mucositis Grading Scale and VAS scale for pain score will be used for daily assessment. The nurses will reinforce and provide assistance to the patients on how to perform the intervention during this period. The patients’ opinions towards the protocol will also be documented with a questionnaire.
for data analysis and evaluation.

The actual cost for carrying out the protocol will be documented and for further budget analysis and evaluation.

6.4 Data Collection and Analysis

Data on the incidence and severity of the patients’ stomatitis collected in these three months will be analyzed and compared with the ward record in order to examine the effectiveness and feasibility of the protocol. The patients’ compliance and opinions towards the intervention will also be recorded in a pre-designed questionnaire. The reasons for patients who quit the pilot study will be documented for later analysis.

Staff acceptance and satisfaction towards the patient recruitment, assessment tools and the protocol can be investigated in this pilot test by conducting questionnaire and focus group to collect their opinions. They will be invited to share their opinions and difficulties during the weekly ward meeting. The effectiveness of the training process and resources support will also be evaluated by observing the logistic of the protocol implementation and collecting staff opinions.
6.5 Evaluation

Through this pilot testing, the potential budget and technical problems of the protocol will be identified and hence modifications can be made. Results of the pilot testing including feasibility and effectiveness of the protocol, technical problems encountered, the suggested solutions, and the compliance of staff will be discussed in the steering committee and shared with frontline staff in ward meeting. The modifications concluded from the evaluation of the pilot study will be used to revise and finalize the protocol for full-scale implementation. The result of the pilot testing as well as the finalized protocol will be reported to the administrators. The timeframe of the program is shown in Appendix 23.
Chapter 7: Evaluation

The aim of an evaluation plan is to verify the success of the protocol and to determine whether the proposed protocol meets the expected outcomes (Mulhall, LeMay, 1999). The outcomes to be evaluated will include the patients’ outcomes, staff satisfaction level, and competency in administrating the protocol, the identification of outcomes, the data analysis plan and the effective criterion of the protocol will be discussed.

7.1 Identifying Outcomes to be Achieved

**Patient outcomes**

The aim of this protocol is to reduce stomatitis rate and severity in patients receiving high dose chemotherapy during HSCT transplantation. The incidence, severity, and pain level of stomatitis are considered to be the primary outcomes in determining the effectiveness of the protocol. The incidence rate and severity of stomatitis is measured daily by the nurses using the WHO Oral Mucositis Grading Scale whereas VAS scale is used for pain level measurement. The measurements will start from the day that chemotherapy starts until the patients are discharged.
The patients’ satisfaction level towards the intervention is considered as the secondary outcome. They will fill in a pre-designed self-developed questionnaire concerning the intervention before discharge (Appendix 24).

**Healthcare provider outcomes**

Healthcare providers’ acceptance and satisfaction level towards the training session, protocol implementation process, and the compliance rate will be evaluated. A pre-designed self-developed questionnaire containing 8 questions concerning the training session and protocol implementation will be distributed to the frontline staff (Appendix 25). The compliance on the protocol will be checked by the Steering Committee by auditing the nursing charts and documentation.

The healthcare providers’ knowledge on stomatitis care will be examined with a self-designed pre-test and post-test questionnaire before and after the protocol implementation.

**System outcomes**

The system outcomes will be measured in terms of the cost-effectiveness of the protocol. Additional cost needed in this protocol will be calculated. It includes the training budget, promotion and information package, and any extra manpower needed.
The material and non-material cost will be calculated at the end of the implementation period and will be compared with the costs of maintaining the usual practice.

7.2 Nature and Number of Patients Involved

The eligibility of patients involved in the evaluation plan is the same as the one of the patients being eligible in the protocol (i.e. patients aged >18 years who are diagnosed with haematological malignancy and are admitted for autologous HSCT in the adult HSCT center).

The number of clients involved in the evaluation plan is determined by the primary outcome, study design, and method of analysis. The incidence and severity of stomatitis is considered as the primary outcome in this study. Forty to 128 patients were recruited in the reviewed studies to investigate the effectiveness of this intervention. Despite the variable sample size among the reviewed studies, they all attained statistically significant outcomes including reduction in stomatitis incidence and severity. Therefore, 150 patients will be recruited in the evaluation plan in order to examine the effectiveness of this new protocol in the proposed setting. According to the center admission record, it will take nine months to recruit 150 patients.
7.3 Data Collection and Analysis

Based on the previous identified studies, patients’ primary outcome on stomatitis can be measured from the day of chemotherapy infusion until day 28 after stem cell infusion. Patients’ data collected will be inputted into computer for analysis. The satisfactory level among patients and healthcare providers, and the system outcome can be evaluated after nine months of protocol implementation. The defined level of significance for the analysis is 0.05 and the confidence interval is 95%.

**Patient outcomes**

The oral condition including stomatitis severity and pain level is assessed and documented by the nurses daily. The incidence rate and severity of stomatitis is measured daily by the WHO Oral Mucositis Grading Scale with (0 = None ; IV = Oral alimentation impossible). The VAS scale is used for pain level measurement (0 = No pain; 5 = Distressing pain; 10 = Unbearable pain).

For patients’ satisfaction level towards the intervention, they will fill in a self-developed questionnaire concerning the intervention before discharge (1 = Strongly agree; 2 = Agree; 3 = Neutral; 4 = Disagree and 5 = Strongly disagree) (Appendix 24). The total score of the questionnaire ranges from 8 to 40. The last question is an open-end question which allows them to express their comments.
Descriptive statistics, means and SD, will be used to represent the data. Comments and suggestions collected will be remarked for future improvements.

**Healthcare provider outcomes**

For healthcare provider satisfaction level, they will also fill in a self-developed questionnaire concerning the intervention (1 = Strongly agree; 2 = Agree; 3 = Neutral; 4 = Disagree and 5 = Strongly disagree) (Appendix 25). The total score of the questionnaire ranges from 8 to 40. The last question is an open-end question which allows them to express their comments. The data collected from questionnaire concerning the training session and protocol implementation will be analyzed. The total score of the questionnaire ranges from 8 to 40. The higher the score, the higher acceptance and satisfaction level among healthcare providers is. The last question is an open-end question which allows them to express their comments. Besides the questionnaire, a focus group will be organized to collect their opinions. Their opinions are valuable for the evaluation in addition to the data analysis.

Staff competency will be assessed by the pre-test and post test questionnaire. The data will be analyzed with t test.
System Outcome

The material and non-material costs in this protocol will be compared with current practice. The protocol will be regarded as successful if the cost of implementing the protocol can cut down 30% cost for maintaining the current practice.

7.4 Effective criterion for the protocol

Stomatitis incidence rate

According to Vokurka et al (2011), the incidence was statistically significantly reduced in the study group as compared with the control group (22% vs. 78%; p <= 0.0001). As reported by Svanberg et al (2007), the incidence rate of stomatitis is 80% which is similar to the situation with HSCT. Therefore, the protocol can be evaluated as successful if the incidence rate is around 70% in the HSCT center after the protocol implementation.

Stomatitis severity

The severity of stomatitis was assessed in all of the six studies (Lilleby et al, 2006; Karagozlu et al, 2004; Salvador et al, 2012; Svanberg et al, 2007, Svanberg et al, 2010, Vokurka et al, 2011). Among the reviewed studies, it was
commonly concluded that only a small percentage of subjects in the study groups developed severe stomatitis and the results were statistically significant among the studies. In Lilleby et al (2006), 14% patients in study group developed grade 3 stomatitis compared with 74% patients in control group (p= 0.0005). In Svanberg et al (2010), patients developing grade 3 -4 stomatitis was 23% - 52% (p <0.05) in study and control group respectively.

The number of patients developed stomatitis of grade 3 or above will be calculated and analyzed. After data analysis, the protocol can be regarded as successful if the percentage of patients developing grade 4 stomatitis is reduced by 20%.

**Pain score**

In the reviewed studies, Lilleby et al (2006) and Salvador et al (2012) reported that pain level experienced by the participants were lower in the study group than in the control group (mean score: 0.41 vs. 1.06; 0.3 vs. 1.64 reported in the two studies respectively). To compare the mean pain score experienced by patients, t test will be used. The new protocol can be evaluated as successful if pain score assessed with VAS is reduced by 1.
Patients and healthcare provider satisfaction level

Patients and healthcare providers’ support towards the protocol is essential. The higher the score, the higher acceptance and satisfaction level among patients and health care providers is. The numeric data will be collected and analyzed with mean and standard deviation. Comments and suggestions collected in the last question as well as the focus group will be remarked for future improvement. It is expected that over 70% of patients and healthcare workers will be satisfy with the protocol.
Chapter 8: Conclusion

Haematological stem cell transplantation (HSCT) is a revolutionary treatment for haematological malignancies. Although HSCT is potentially curative, patients usually develop stomatitis which is a common and debilitating complication after the transplantation. Furthermore, stomatitis may predispose patients to various complications which are associated with significantly increased morbidity and mortality.

A well established protocol can help to minimize the patients’ suffering and avoid prolonged hospitalization. The nurses who are involved in patient education, assessment, care for, and coping with stomatitis, play an important role to bring these innovations into practice. The nurses who are involved in patient education, assessment, care for, and coping with stomatitis, play an important role to bring these innovations into practice. In some studies, ice water mouthwash has been shown to be an effective method for the prevention of stomatitis. However, conclusive high-level evidence of its efficacy and well-established protocols are not fully developed at present and it is not commonly practiced in most medical centers including the proposed settings. In this regard, a systematic, critical and
evidence-based guideline of the related issue has been generated. The relevant evidence from the reviewed study was used to establish the protocol for patients in the proposed settings, and well-designed implementation and evaluation plans were suggested. The proposed protocol is transferable and feasible for the target settings and audience. Good communication skills as well as a clearly written protocol are definitely critical for the successful implementation of the proposed protocol throughout the different phases.

The successful implementation of the protocol for the prevention of stomatitis using oral cryotherapy will be beneficial to the patients undergoing HSCT as it may hasten their recovery, shorten their hospital stay, and minimize their distressing experience and suffering. Therefore, further clinical trials are urgently needed for this potentially useful, cost-effective, and relatively harmless intervention.
### Appendix 1: Summary of search result

<table>
<thead>
<tr>
<th>Database</th>
<th>PubMed</th>
<th>CLINAHL Plus (EBSCO HOST)</th>
<th>ProQuest</th>
<th>ScienceDirect</th>
<th>Medline (OvidSP)</th>
</tr>
</thead>
<tbody>
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<td>05/09/2012</td>
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<td>Suitable literatures</td>
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### Appendix 2: Summary of search - PubMed

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<td>#4</td>
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<tr>
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<td>((ice water) OR cryotherapy) OR ice cube gargling</td>
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<td>((stomatitis) OR mucositis)) OR oral complication</td>
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### Appendix 3: Summary of search - CLINAHL Plus (EBSCO HOST)

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<td>S2</td>
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<td>S1</td>
<td>Stomatitis OR mucositis</td>
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## Appendix 4: Summary of search – ProQuest

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<td>all((mucositis OR Stomatitis)) AND all((cryotherapy OR ice water))</td>
<td>Population, Female, Human, Male, Age group, Adulthood (18 Yrs &amp; Older), Aged (65 Yrs &amp; Older), Middle Age (40-64 Yrs), Thirties (30-39 Yrs), Young Adulthood (18-29 Yrs)</td>
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## Appendix 5: Summary of search - ScienceDirect

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<td>(stomatitis or mucositis) and (cryotherapy)</td>
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### Appendix 6: Summary of search – Medline (Ovid)

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Appendix 7: Table of evidence (1)

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<th>Name</th>
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<th>Subject Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Length of FU</th>
<th>Outcome Measures</th>
<th>Effect Size</th>
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<tr>
<td>Karagoğlu et al, 2004</td>
<td>RCT</td>
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<td>Moving rounded ice cube in mouth constantly initiated 5 minutes before chemotherapy and maintained during the chemo infusion (n= 30)</td>
<td>Patients received chemo-therapy without cryotherapy and other preventive measure (n = 30)</td>
<td>On 1st, 2nd, 3rd &amp; 21th days after chemo-therapy</td>
<td>1. Patient-Judged Mucositis Grading (0-4)</td>
<td>1. 36.7% vs 90% (p &lt;0.05)</td>
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<td></td>
<td>2. Physician-Judged Mucositis Grading (0-4)</td>
<td>2. 10% vs 50% (p &lt; 0.05)</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>3. Oral pH Measurement (6.3 – 7.2)</td>
<td>Highest mean score: 0.23 vs 0.83</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary measure: 1. Mean duration of mucositis</td>
<td>3. Decrease 90% in study group (p &lt; 0.05)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Secondary outcome: 1. 7.09 days vs 12.03 days (p &lt; 0.05)</td>
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Appendix 8: Table of evidence (2)

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<th>Control</th>
<th>Length of FU</th>
<th>Outcome Measure</th>
<th>Effect Size</th>
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</table>
| Lilleby et al, 2006 | RCT      | 1-             | 41 multiple myeloma patients
Scheduled to receive melphalan 200mg/m2 undergoing autologous stem cell transplantation
>18 years old Age range: 33 -72 Median age: 59 vs 57 | Place 1 once crushed ice chips rinse 30 min before melphalan infusion and 6hr after end of infusion every 30min (n= 21) | Room temperatur e normal saline rinse 30 min before melphalan infusion and 6hr after end of infusion every 30min (n= 21) | Day 2 to day 28 | 1. Questionnaire of oral condition 2. Pain score (0-10) 3. NCI mucositis grade (0-4) | 1. Average number of days which patients reported for sore of mouth was similar
2. Mean of scores: 0.41 vs 1.06 (p= 0.0005)
3. Patients developed grade 3 mucositis: 14% vs 74% (p= 0.0005) | 1. Secondary Measure:
1. Number of days with grade 3 mucositis
2. Days of TPN (0-21)
3. Days of iv. Narcotics (0-13)
4. Days of hospitalization (0-30)
5. Weight loss (06 -9.8)
6. 1st day 30% of caloric needs met (2-48) | 1. 0.5 days vs 4.6 days (p = 0.0001)
2. 2 vs 5.5 (p =0.04)
3. 0 vs 5.5 (p=0.0003)
4. 9 vs 14 (p = 0.11)
5. 3.9 vs 5
6. 14.5 vs 16 |
## Appendix 9: Table of evidence (3)

<table>
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<th>Name</th>
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<th>Evidence Level</th>
<th>Subject Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Length of FU</th>
<th>Outcome Measure</th>
<th>Effect Size</th>
</tr>
</thead>
</table>
| Salvador et al, 2012 | Prospective, pilot, RCT | 1++            | • Age range: 43-72 Mean age: 56 vs 62  
• Higher mean age & education in EXP. Group  
• No. sig. diff. in gender & smoking & alcohol  
• Multiple myeloma patients receive high dose melphalan (200 mg/m2)  
• No existing oral disease and had radiotherapy to head and neck region were excluded | Sucked on two teaspoons of ice chips 5 minutes before, during, and after the chemotherapy for a total of 60 minutes. Swirl around the ice chips in their mouths, and keep on taking the ice chips before melting. (n = 23) | Standard oral care includes  
1) Tooth brushing with Toothette sponges  
2) Mouth rinsing with sodium bicarbonate mouthwash  
3) Applying moisturizer to lips or oral cavity as needed (n= 23) | Day 3, 6, 9 & 12 after stem cell transplant | 1. Time of onset  
2. Severity/duration  
3. Resolution  
4. WHO mucositis grading scale (0-4) | Secondary outcomes  
1. Pain level (VAS 0-10)  
2. Intake of food & fluid (nutritional assessment form) (0-5)  
3. Length of stay  
4. Tolerability of cryotherapy  
5. Amount of morphine used | Secondary outcomes  
1. 5-7 days  
2. 6 days  
3. 12 days  
4. Overall mean OM scores = 0.71  
0.43 vs 1.14 |
### Appendix 10: Table of evidence (4)

<table>
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<th>Name</th>
<th>Study Design</th>
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<th>Subject Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Length of FU</th>
<th>Outcome Measure</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svanberg et al, 2007</td>
<td>RCT</td>
<td>1+</td>
<td>- 78 patients scheduled for bone marrow transplant&lt;br&gt;- &gt;18 years old&lt;br&gt;- 2 patients had testicular cancer; all others had hematological malignancies.&lt;br&gt;- No significant differences in gender, age or tobacco use &amp; chemotherapy or irradiation</td>
<td>Started oral cryotherapy less than 5 mins before chemotherapy&lt;br&gt;Suck on ice chips or rinse with cold water during chemotherapy administration (n= 39)</td>
<td>Standard oral care includes oral cavity examination and necessary dental treatment before chemo-therapy Soft toothbrush and gentle toothpaste provided (n= 39)</td>
<td>Till day 21</td>
<td>1. Visual analogue scale (VAS)(0-10)&lt;br&gt;2. Oral Mucositis Assessment score (OMAS)&lt;br&gt;3. Number of days and dose of opioids&lt;br&gt;4. CRP at Day 11</td>
<td>For autologous transplantation&lt;br&gt;1. Mucositis score on day 10 (1.6±1.9 vs 4.3±5.7; p=0.042)&lt;br&gt;2. Days with opioids (0.06±0.25 vs 1.71±3.22, p=0.008)&lt;br&gt;3. Total dose of opioids (1.45±5.9 vs 162±376 mg, p=0.024)&lt;br&gt;Number of days with opioids (0.77±2.3 vs 2.44±4.6, p=0.045)&lt;br&gt;4. CRP at Day 20 (66.1 ± 54.6 vs 111.3±99.1, p=0.039)</td>
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Appendix 11: Table of evidence (5)

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<th>Name</th>
<th>Study Design</th>
<th>Evidence Level</th>
<th>Subject Characteristics</th>
<th>Intervention</th>
<th>Control</th>
<th>Length of FU</th>
<th>Outcome Measure</th>
<th>Effect Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svanberg et al, 2010</td>
<td>RCT</td>
<td>1+</td>
<td>- 78 patients scheduled for bone marrow transplant&lt;br&gt;- &gt;18 years old&lt;br&gt;- Mean age: 49.8 vs 54.3&lt;br&gt;- 2 patients had testicular cancer; all others had hematological malignancies.&lt;br&gt;- No significant differences with regard to gender, age or tobacco use &amp; chemotherapy or irradiation</td>
<td>Started oral cryotherapy less than 5 mins before chemotherapy&lt;br&gt;Suck on ice chips or rinse with cold water during chemotherapy administration (n= 39)</td>
<td>Standard oral care includes oral cavity examination and necessary dental treatment (n= 39)</td>
<td>Mucositis was assessed during 21 days and others during 31 days</td>
<td>1. Oral mucositis assessment score (OMAS) (0-4)&lt;br&gt;2. Temperature&lt;br&gt;Infection rare by neutropenic fever &amp; iv Antibiotics&lt;br&gt;3. Nutrition by weight, TPN administration&lt;br&gt;S-albumin (37- 48g/l)</td>
<td>For autologous HSCT&lt;br&gt;1. Mucositis grade 3-4: 23% vs. 52% (p &lt;0.05)&lt;br&gt;2. Mean no. of days at hospital: 7 vs. 4.4 days&lt;br&gt;3. No. of patients receiving TPN: 32 vs 45&lt;br&gt;4. Mean no. of days with TPN: 4.5 vs 4.6&lt;br&gt;5. Mean no of days with fever: 6 vs 5.6&lt;br&gt;6. No. of patients receiving antibiotics: 52 vs 55</td>
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### Appendix 12: Table of evidence (6)

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<th>Name</th>
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<th>Intervention</th>
<th>Control</th>
<th>Length of follow up</th>
<th>Outcome Measure</th>
<th>Results</th>
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</table>
| Vokurka et al, 2011  | Cohort study | 2+             | * 128 patients with hematological disease treated with high dose BEAM or HD-L_PAM 200mg/m² chemotherapy followed by autologous HSCT  
* Age>18 years old (Range:18-67)  
* Median age: 57  
* Had healthy oral mucosa  
* No history of head or neck or total body radiotherapy  | Ice lollipops, ice-coldwater or crushed ice cryotherapy started 5 min before the melphalan administration, during and 15 min afterwards. Patients keep the ice or water in their mouth, to gargle it, spit it out (n=36)  | After meal and before sleep mouthwashes and 2 min gargling with solutions, e.g. Chlorhexidine Salvia officinalis Povidoneiiodine Normal saline Listerine Johnson & Johnson Benzydamine Water for infusions Dental cleaning with soft toothbrush 2 times/day (n= 90) | Start on day of chemo-therapy till discharged  | WHO grading (0-4)  
Tolerability of cryotherapy  
VAS score (1-5)  | Incidence of OM: 22% vs. 78% (p<= 0.0001)  
OM grade 1: 35% vs. 19%  
OM grade 2: 19% vs. 0%  
OM grade 3: 21% vs. 3%  
OM grade 4: 2% vs. 0%  
Median duration: 5days vs. 3 days  
Resolved on day: +10 vs. +8  
Tolerability of cryotherapy  
VAS 1: 88%  
VAS 2: 9%  
VAS 3: 3%  
VAS 4: 0%  
VAS 5: 0% |

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<tbody>
<tr>
<td>1.</td>
<td>The study addresses an appropriate and clearly focused question.</td>
<td><strong>Well covered</strong> -- The research question was addressed clearly and appropriately.</td>
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<tr>
<td>2.</td>
<td>The assignment of subjects to treatment groups is randomised</td>
<td><strong>Adequately addressed</strong> -- 5 patients were assigned to study group and the next 5 patients were assigned to control group.</td>
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<td>3.</td>
<td>An adequate concealment method is used</td>
<td><strong>Not reported</strong></td>
</tr>
<tr>
<td>4.</td>
<td>Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td><strong>Not reported</strong></td>
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<tr>
<td>5.</td>
<td>The treatment and control groups are similar at the start of the trial</td>
<td><strong>Adequately addressed</strong> -- The participants’ background is addressed. 76.7% were male and 66.7% &gt; 60 years old</td>
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<tr>
<td>6.</td>
<td>Only difference between groups is the treatment under investigation</td>
<td><strong>Poorly addressed</strong> -- No additional treatment received by / provided to participants was reported</td>
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<tr>
<td>7.</td>
<td>All outcomes are measured in a standard, valid and reliable way</td>
<td><strong>Well covered</strong> -- The justification of primary outcome measure was provided</td>
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<tr>
<td>8.</td>
<td>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td><strong>Not reported</strong></td>
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<tr>
<td>9.</td>
<td>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td><strong>Not addressed</strong></td>
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<td>10.</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
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<td>11.</td>
<td>How well was the study done to minimize bias? Code ++, +, or -</td>
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## Appendix 14: SIGN Checklist for RCT Studies (2): Lilleby et al, 2006

| 1. The study addresses an appropriate and clearly focused question. | **Well covered** -- The research question was addressed clearly and appropriately. |
| 2. The assignment of subjects to treatment groups is randomised | **Adequately addressed** – Subjects were stratified then randomized |
| 3. An adequate concealment method is used | **Not addressed** |
| 4. Subjects and investigators are kept ‘blind’ about treatment allocation | **Not addressed** |
| 5. The treatment and control groups are similar at the start of the trial | **Adequately addressed** – Participants have similar age and diagnosis |
| 6. The only difference between groups is the treatment under investigation | **Poorly addressed** – No additional treatment received by / provided to participants was reported |
| 7. All relevant outcomes are measured in a standard, valid and reliable way | **Poorly addressed** – Questionnaire used was not stated |
| 8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed? | **Drop-out rate in control group** -- 1/ 41 x 100% = 2.44% |
| 9. All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis) | **Not reported** – The drop out data was not analyzed in the study |
| 10. Where the study is carried out at more than one site, results are comparable for all sites | **Not addressed** |
| 11. How well was the study done to minimize bias? Code ++, +, or - | - |

<p>| | |</p>
<table>
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<tbody>
<tr>
<td>1. The study addresses an appropriate and clearly focused question.</td>
<td><strong>Well covered</strong> -- The research question was addressed clearly and appropriately.</td>
</tr>
<tr>
<td>2. The assignment of subjects to treatment groups is randomised</td>
<td><strong>Well covered</strong> – Using computer generated random number list</td>
</tr>
<tr>
<td>3. An adequate concealment method is used</td>
<td><strong>Well covered</strong> – Sealed envelopes were used</td>
</tr>
<tr>
<td>4. Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td><strong>Adequately addressed</strong> – Research assistants who collected data were blinded</td>
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<tr>
<td>5. The treatment and control groups are similar at the start of the trial</td>
<td><strong>Well covered</strong> – Higher mean age in study group; No significant different in gender, smoking and drinking status</td>
</tr>
<tr>
<td>6. The only difference between groups is the treatment under investigation</td>
<td><strong>Not reported</strong> – No additional treatment received by / provided to participants was reported</td>
</tr>
<tr>
<td>7. All relevant outcomes are measured in a standard, valid and reliable way</td>
<td><strong>Adequately addressed</strong> – Assessment scale with justified WHO grading scale and VAS for stomatitis severity and pain</td>
</tr>
<tr>
<td>8. What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td><strong>Drop-out rate in control group:</strong> 1 / 46 x 100% = 2.17%</td>
</tr>
<tr>
<td>9. All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td><strong>Poorly addressed</strong> – The drop out data was not analyzed in the study</td>
</tr>
<tr>
<td>10. Where the study is carried out at more than one site, results are comparable for all sites</td>
<td><strong>Not reported</strong></td>
</tr>
<tr>
<td>11. How well was the study done to minimise bias? Code ++, +, or -</td>
<td>++</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q</th>
<th>Description</th>
<th>Rating</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>The study addresses an appropriate and clearly focused question.</td>
<td><strong>Well covered</strong> -- The research question was addressed clearly and appropriately.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>The assignment of subjects to treatment groups is randomised</td>
<td><strong>Adequately addressed</strong> – Done with block of six and stratified randomization</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>An adequate concealment method is used</td>
<td><strong>Not reported</strong></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td><strong>Poorly addressed</strong></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>The treatment and control groups are similar at the start of the trial</td>
<td><strong>Adequately addressed</strong> – Besides 2 patients suffered from testicular cancer, all patients had haematological malignancies</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>The only difference between groups is the treatment under investigation</td>
<td><strong>Not reported</strong> – No additional treatment received by / provided to participants was reported</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>All relevant outcomes are measured in a standard, valid and reliable way</td>
<td><strong>Poorly addressed</strong> – Well justified measurement scale such as VAS and OMAS adopted</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td><strong>Drop-out rate</strong> = 3/80 x 100% = 3.75%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td><strong>Well covered</strong> – Intention to treat analysis adopted</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
<td><strong>Not reported</strong></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>How well was the study done to minimize bias? Code ++, +, or -</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
**Appendix 17: SIGN Checklist for RCT Studies (5): Svanberg et al, 2010**

<table>
<thead>
<tr>
<th></th>
<th>The study addresses an appropriate and clearly focused question.</th>
<th>Well covered -- The research question was addressed clearly and appropriately.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>The assignment of subjects to treatment groups is randomised</td>
<td>Well covered – Done with block of six and stratified randomization</td>
</tr>
<tr>
<td>3.</td>
<td>An adequate concealment method is used</td>
<td>Not reported</td>
</tr>
<tr>
<td>4.</td>
<td>Subjects and investigators are kept ‘blind’ about treatment allocation</td>
<td>Poorly addressed</td>
</tr>
<tr>
<td>5.</td>
<td>The treatment and control groups are similar at the start of the trial</td>
<td>Adequately addressed – Besides 2 patients suffered from testicular cancer, all patients had haematological malignancies</td>
</tr>
<tr>
<td>6.</td>
<td>The only difference between groups is the treatment under investigation</td>
<td>Not reported – No additional treatment received by / provided to participants was reported</td>
</tr>
<tr>
<td>7.</td>
<td>All relevant outcomes are measured in a standard, valid and reliable way</td>
<td>Poorly addressed – Well justified measurement scale such as VAS and OMAS adopted</td>
</tr>
<tr>
<td>8.</td>
<td>What percentage of the individuals or clusters recruited into each treatment arm of the study dropped out before the study was completed?</td>
<td>Drop-out rate : 3/80x 100% = 3.75%</td>
</tr>
<tr>
<td>9.</td>
<td>All the subjects are analysed in the groups to which they were randomly allocated (often referred to as intention to treat analysis)</td>
<td>Well covered – Intention to treat analysis adopted</td>
</tr>
<tr>
<td>10.</td>
<td>Where the study is carried out at more than one site, results are comparable for all sites</td>
<td>Not reported</td>
</tr>
<tr>
<td>11.</td>
<td>How well was the study done to minimise bias? Code ++, +, or -</td>
<td>+</td>
</tr>
</tbody>
</table>
### Appendix 18: SIGN Checklist for Cohort Studies: Vokurka et al, 2011

<table>
<thead>
<tr>
<th></th>
<th>The study addresses an appropriate and clearly focused question.</th>
<th>Well covered -- The research question was addressed clearly and appropriately</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.</td>
<td>Well covered -- Diagnosis, background and treatment of participants were clearly stated</td>
</tr>
<tr>
<td>3</td>
<td>The study indicates how many people asked to take part, in each of the groups being studied.</td>
<td>Not addressed</td>
</tr>
<tr>
<td>4</td>
<td>The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.</td>
<td>Not addressed</td>
</tr>
<tr>
<td>5</td>
<td>What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.</td>
<td>Drop-out rate: 2/128 x 100% = 1.56%</td>
</tr>
<tr>
<td>6</td>
<td>Comparison is made between full participants and those lost to follow up, by exposure status.</td>
<td>Not addressed</td>
</tr>
<tr>
<td>7</td>
<td>The outcomes are clearly defined.</td>
<td>Well covered -- The severity of stomatitis and tolerability of cryotherapy was assessed</td>
</tr>
<tr>
<td>8</td>
<td>The assessment of outcome is made blind to exposure status.</td>
<td>Not addressed</td>
</tr>
<tr>
<td>9</td>
<td>Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.</td>
<td>Not addressed</td>
</tr>
<tr>
<td>10</td>
<td>The measure of assessment of exposure is reliable.</td>
<td>Well covered -- The compliance is good and the subjects in intervention group adhered to the intervention</td>
</tr>
<tr>
<td>Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.</td>
<td><strong>Adequately addressed</strong> – WHO grading and VAS is adopted</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Exposure level or prognostic factor is assessed more than once.</td>
<td><strong>Well covered</strong></td>
<td></td>
</tr>
<tr>
<td>The main potential confounders are identified and taken into account in the design and analysis.</td>
<td><strong>Adequately addressed</strong> – The confounders were put into further analysis in the study</td>
<td></td>
</tr>
<tr>
<td>Have confidence intervals been provided?</td>
<td><strong>Yes</strong></td>
<td></td>
</tr>
<tr>
<td>How well was the study done to minimise the risk of bias or confounding, and to establish a causal relationship between exposure and effect? <em>Code ++, +, or -</em></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 19 -- Grades of Recommendation by Scottish Intercollegiate Guidelines Network (SIGN) 2011

Levels of evidence

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1++</td>
<td>High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias</td>
</tr>
<tr>
<td>1+</td>
<td>Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias</td>
</tr>
<tr>
<td>1-</td>
<td>Meta-analyses, systematic reviews, or RCTs with a high risk of bias</td>
</tr>
<tr>
<td>2++</td>
<td>High quality systematic reviews of case control or cohort or studies</td>
</tr>
<tr>
<td></td>
<td>High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal</td>
</tr>
<tr>
<td>2+</td>
<td>Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal</td>
</tr>
<tr>
<td>2-</td>
<td>Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal</td>
</tr>
<tr>
<td>3</td>
<td>Non-analytic studies, e.g. case reports, case series</td>
</tr>
<tr>
<td>4</td>
<td>Expert opinion</td>
</tr>
</tbody>
</table>

Grades of recommendation

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target</td>
</tr>
<tr>
<td>B</td>
<td>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1++ or 1+</td>
</tr>
<tr>
<td>C</td>
<td>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2++</td>
</tr>
<tr>
<td>D</td>
<td>Evidence level 3 or 4; or extrapolated evidence from studies rated as 2+</td>
</tr>
</tbody>
</table>
### Appendix 20 -- WHO Oral Mucositis Grading Scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (none)</td>
<td>None</td>
</tr>
<tr>
<td>I (mild)</td>
<td>Oral soreness, erythema</td>
</tr>
<tr>
<td>II (moderate)</td>
<td>Oral erythema, ulcers, solid diet tolerated</td>
</tr>
<tr>
<td>III (severe)</td>
<td>Oral ulcers, liquid diet only</td>
</tr>
<tr>
<td>IV (life-threatening)</td>
<td>Oral alimentation impossible</td>
</tr>
</tbody>
</table>
### Appendix 21 – Costs of establishing the protocol for 10 patients for 3 months

<table>
<thead>
<tr>
<th>Items</th>
<th>Estimated Cost (HK$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equipment (Plastic cups)</td>
<td>$ 5 x 10 patients = $50</td>
</tr>
<tr>
<td>Pamphlets to patients</td>
<td>$ 5 x 20 patients x 3 months = $300</td>
</tr>
<tr>
<td>Registered nurse training time</td>
<td>$ 200 (hourly paid) x 1 hour x 14 staff = $2800</td>
</tr>
<tr>
<td>Staff training materials</td>
<td>~ $50</td>
</tr>
<tr>
<td>(e.g. photocopying and training</td>
<td></td>
</tr>
<tr>
<td>notes)</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$3200</strong></td>
</tr>
</tbody>
</table>

**Remarks:**

1. There are 10 plastic cups available for patients in the ward. Ten additional plastic cups are purchased for replacement.

2. According to the statistics in the ward, there are around 20 patients admitted to HSCT center every 3 months. Pamphlets with instructions of the intervention will be clearly demonstrated.

3. Mean salary of a registered nurse per hours = HKD 200

4. Training notes including the intervention details, rationales, evaluation method, and potential problems will be provided to staff.

5. Venue for holding staff training is provided by the hospital.
Appendix 22 – Costs of taking care of one patient with severe oral stomatitis per week

<table>
<thead>
<tr>
<th>Items</th>
<th>Estimated Cost (HK$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization fee (bed, physician round, nursing care)</td>
<td>^$ 23100</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>* $ 2900</td>
</tr>
<tr>
<td>Medications (e.g. pain killer)</td>
<td>@ $ 24.5</td>
</tr>
<tr>
<td>Total parental nutrition</td>
<td># $ 2513</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$ 28537.5</strong></td>
</tr>
</tbody>
</table>

Remarks:

^ Hospitalization fee (bed, physician round, nursing care) is $3300/ day x 7 = $23100

* Antibiotics commonly used in HSCT setting range from $ 22.6 – 184.5;

Average = $ 103.6

Antibiotics usually administered as Q6h for one week:

Cost = $ 103.6 x 4 doses x 7 days = $ 2900

# Total parental nutrition = Structokabiven (or equiv) inf. 1477ml + Addamel N 10ml

+ Soluvit N 10ml = $278 + $36 + $45 = $ 359 x 7 days = $ 2513

@ Morphine sulphate inj. 15ml/ml 1ml = $3.5/ amp x 7 days = $ 24.5

Assuming that there are 15 patients who can benefit from the protocol in these 3 months, the total cost reduction will be $28537.5 x 15 = $ 428062.5
# Appendix 23 – Implementation schedule for the protocol

<table>
<thead>
<tr>
<th>Event</th>
<th>Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seek approval from DOM, WM, physicians &amp; nurses</td>
<td>2</td>
</tr>
<tr>
<td>Allow for feedback &amp; amendment</td>
<td>3</td>
</tr>
<tr>
<td>Staff briefing &amp; training</td>
<td>3</td>
</tr>
<tr>
<td>Pilot test</td>
<td>4-6</td>
</tr>
<tr>
<td>Protocol improvement</td>
<td>7-10</td>
</tr>
<tr>
<td>Implementation of the protocol</td>
<td>11-15</td>
</tr>
<tr>
<td>Patient evaluation</td>
<td>11-15</td>
</tr>
<tr>
<td>Staff evaluation</td>
<td>11-15</td>
</tr>
</tbody>
</table>
Appendix 24: Patients evaluation form

Ice water mouthwash for patients undergoing Autologous HSCT

Evaluation Form

Please “tick” the following:

1 = Strongly disagree;  2 = Disagree;  3 = Neutral;  4 = Agree;  5 = Strongly agree

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. The ice water mouthwash is useful to minimize chemotherapy induced oral stomatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. The new intervention is easy to understand and follow</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Nurses are always available for enquiry when needed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Nurses are knowledgeable about the new treatment care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The instruction from nurses for the new intervention is sufficient and useful</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. The new treatment care does not induce much discomfort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. You are willing to use the new treatment care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. You are satisfy with the new intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Any other comment? (e.g. suggestion, etc)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 25: Healthcare providers evaluation form

Ice water mouthwash for patients undergoing Autologous HSCT

Evaluation Form

Please “tick” the following:

1 = Strongly disagree;  2 = Disagree;  3 = Neutral;  4 = Agree;  5 = Strongly agree

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Support/ resources for the protocol implementation is enough</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Patients can benefit from the new protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Adequate training/ instruction for the protocol is provided</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Extra heavy workload and time is added to daily routine care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. The innovation can elevate nurses’ morale and job satisfaction during protocol implementation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. You feel confident in conducting the protocol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Knowledge towards taking care of patients with stomatitis increased</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. The protocol is worth implementing in the center in long term</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

9. Any other comment? (e.g. suggestion, etc)

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
References


