

## APPENDIX 2: SEARCH STRATEGIES, SELECTION CRITERIA AND APPRAISAL

### a) Randomized Controlled Trials of Cryotherapy

- i. **Search Strategy:** The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.
- ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers that were randomized controlled trials (RCTs) or quasi-RCTs of cryotherapy for the prevention of mucositis in patients receiving treatment for cancer or undergoing hematopoietic stem cell transplantation (HSCT). There was no restriction by language. Two reviewers compiled the evidence summary table.

#### MEDLINE: The search strategy for OvidSP MEDLINE (1946 to April 1, 2014)

Set	History
1	mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab.
2	exp neoplasms/ or exp Antineoplastic Agents/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation dosage/ or dose-response relationship, radiation/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or rt.fs. or radiotherapy/ or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	1 and 2
4	cryotherapy/ or hypothermia, induced/ or cryosurgery/ or (((cryosurg* or cryogenic*) adj2 (treat* or therap*)) or cryothermy or cryotreat* or (cold adj2 therap*) or cryotherap* or (Oral adj2 cooling)).mp.
5	3 and 4

#### EMBASE: The search strategy for OvidSP Embase Classic+Embase <1947 to 2014 Week 13>

Set	History
1	mucosa inflammation/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp antineoplastic agent/ or exp transplantation/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	1 and 2
4	cryotherapy/ or cryoablation/ or cryosurgery/ or cryosurgery device/ or cryoprobe/ or (((cryosurg* or cryogenic*) adj2 (treat* or therap*)) or cryothermy or cryotreat* or (cold adj2 therap*) or cryotherap* or (Oral adj2 cooling)).mp.
5	3 and 4

**EBM Reviews – CCTR:** The search strategy for OvidSP EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>

Set	History
1	mucosa inflammation/ or mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab. or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*)) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp neoplasms/ or exp antineoplastic agent/ or exp Antineoplastic Agents/ or exp transplantation/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiation dosage/ or dose-response relationship, radiation/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	1 and 2
4	cryotherapy/ or hypothermia, induced/ or cryoablation/ or cryosurgery/ or cryosurgery device/ or cryoprobe/ or (((cryosurg* or cryogenic*) adj2 (treat* or therap*)) or cryothermy or cryotreat* or (cold adj2 therap*) or cryotherap* or (Oral adj2 cooling)).mp.
5	3 and 4

**(b) Randomized Controlled Trials of Low Level Light Therapy (LLLT):** A systematic review of RCTs evaluating LLLT to prevent mucositis in adults and children was recently published.[1]

- i. **Search Strategy:** The following databases were searched and included articles indexed as of February 17, 2014: Ovid in MEDLINE, EMBASE, EBM Reviews – Cochrane Central Register of Controlled Trials, Web of Science, SCOPUS and LILACS. The search strategies may be found in Oberoi et al.[1]
- ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. Studies were included if the population consisted of patients with cancer or undergoing HSCT and patients were randomly assigned to receive prophylactic LLLT versus placebo, no therapy or usual care. Studies were excluded if: (1) allocation not randomly assigned; (2) absence of a placebo or no treatment group; (3) randomized chemotherapy cycles or left and right buccal mucosa within a patient rather than randomizing patients (as episodes would not be independent); and (4) duplicate publication. Studies included in the meta-analysis were not restricted by language or publication status.

**(c) Randomized and Non-Randomized Trials of Keratinocyte Growth Factor (KGF)**

**Randomized Studies of KGF in Adult and Pediatric Populations:**

- i. **Search Strategy:** The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.
- ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers that were RCTs or quasi-RCTs of KGF for the prevention of mucositis in patients receiving treatment for cancer or undergoing HSCT. There was no restriction by language. Two reviewers compiled the evidence summary table.

**Non-Randomized Studies of KGF Conducted in Pediatric Populations:**

- i. **Search Strategy:** The same search strategy to identify RCTs of KGF was used since a filter for trial design was not added.
- ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers of any study design that evaluated KGF for the prevention of mucositis in pediatric patients ( $\leq 25$  years of age) receiving treatment for cancer or undergoing HSCT. There was no restriction by language.

**MEDLINE:** The search strategy for OvidSP MEDLINE (1946 to April 1, 2014)

Set	History
1	mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab.
2	exp neoplasms/ or exp Antineoplastic Agents/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation dosage/ or dose-response relationship, radiation/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or rt.fs. or radiotherapy/ or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1").mp. or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2).mp. or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth) or palifermin or kepivance or "cg 53135" or cg53135 or "recombinant FGF 20" or velafermin).mp. or fibroblast growth factors/ or fibroblast growth factor 1/ or fibroblast growth factor 2/ or fibroblast growth factor 7/ or fibroblast growth factor 10/ or ("recombinant fibroblast growth factor 10" or "KGF 2" or repifermin).mp. or ("FGF 10" or FGF10).mp.
4	1 and 2 and 3

**EMBASE:** The search strategy for OvidSP Embase Classic+Embase <1947 to 2014 Week 13>

Set	History
1	mucosa inflammation/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp antineoplastic agent/ or exp transplantation/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	growth factor/ or fibroblast growth factor/ or fibroblast growth factor 1/ or fibroblast growth factor 10/ or fibroblast growth factor 2/ or keratinocyte growth factor/ or repifermin/ or ("recombinant fibroblast growth factor 10 " or KGF 2 or repifermin).mp. or velafermin/ or ("cg 53135" or cg53135 or "recombinant FGF 20" or velafermin).mp. or palifermin/ or (palifermin or kepivance).mp. or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth)).mp. or ("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1").mp. or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2).mp. or repifermin/ or ("recombinant fibroblast growth factor 10 " or "KGF 2" or kgf2 or repifermin).mp. or ("FGF 10" or FGF10).mp.
4	1 and 2 and 3

**EBM Reviews – CCTR:** The search strategy for OvidSP EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>

Set	History
1	mucosa inflammation/ or mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab. or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*)) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp neoplasms/ or exp antineoplastic agent/ or exp Antineoplastic Agents/ or exp transplantation/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiation dosage/ or dose-response relationship, radiation/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1" or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2) or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth) or palifermin or kepivance or "cg 53135" or cg53135 or "recombinant FGF 20" or velafermin)).mp. or fibroblast growth factors/ or fibroblast growth factor 1/ or fibroblast growth factor 2/ or fibroblast growth factor 7/ or fibroblast growth factor 10/ or ("recombinant fibroblast growth factor 10" or "KGF 2" or repifermin).mp. or ("FGF 10" or FGF10).mp. or growth factor/ or fibroblast growth factor/ or fibroblast growth factor 1/ or fibroblast growth factor 10/ or fibroblast growth factor 2/ or keratinocyte growth factor/ or repifermin/ or ("recombinant fibroblast growth factor 10 " or KGF 2 or repifermin).mp. or velafermin/ or ("cg 53135" or cg53135 or "recombinant FGF 20" or velafermin).mp. or palifermin/ or (palifermin or kepivance).mp. or ("FGF 7" or KGF or "7 fibroblast growth factor" or (keratinocyte adj2 growth)).mp. or ("fibroblast growth factor*" or fgf1 or "hbgf-1" or "fgf-1").mp. or ("fgf 2" or "fgf-2" or fgf2 or prostatropin or hbgf-2).mp. or repifermin/ or ("recombinant fibroblast growth factor 10 " or "KGF 2" or kgf2 or repifermin).mp. or ("FGF 10" or FGF10).mp.
4	1 and 2 and 3

**(d) Randomized Controlled Trials of Any Intervention in Pediatric Patients**

- i. **Search Strategy:** The following databases were searched and included articles indexed as of April 1, 2014: Ovid in MEDLINE, EMBASE, and EBM Reviews – Cochrane Central Register of Controlled Trials.
- ii. **Selection Criteria and Appraisal:** Two reviewers independently evaluated the titles and abstracts of the publications identified by the search strategy. Any publication considered potentially relevant by either reviewer was retrieved in full and assessed for eligibility. Inclusion of studies in this systematic review was determined by agreement of both reviewers. We included fully-published papers that were RCTs or quasi-RCTs of any intervention for the prevention of mucositis in pediatric patients (≤ 25 years of age) receiving treatment for cancer or undergoing HSCT. There was no restriction by language. Two reviewers compiled the evidence summary table.

**MEDLINE:** The search strategy for OvidSP MEDLINE (1946 to **April 1, 2014**)

Set	History
1	mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*)) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab.
2	exp neoplasms/ or exp Antineoplastic Agents/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation dosage/ or dose-response relationship, radiation/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or

	Radiotherapy, Adjuvant/ or rt.fs. or radiotherapy/ or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	randomized controlled trial.pt. or controlled clinical trial.pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.
4	exp animals/ not humans.sh.
5	3 not
6	1 and 2 and 5
7	limit 6 to "all child (0 to 18 years)"
8	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
9	7 or (6 and 9)

**EMBASE:** The search strategy for OvidSP Embase Classic+Embase <1947 to 2014 Week 13>

Set	History
1	mucosa inflammation/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp antineoplastic agent/ or exp transplantation/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	ct.fs. or controlled clinical trial.pt. or controlled clinical trial/ or randomized controlled trial.pt. or randomized controlled trial/ or randomized.ab. or placebo.ab. or dt.fs. or randomly.ab. or trial.ab. or groups.ab.
4	1 and 2 and 3
5	limit 4 to (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>)
6	infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
7	5 or (4 and 6)

**EBM Reviews – CCTR:** The search strategy for OvidSP EBM Reviews - Cochrane Central Register of Controlled Trials <January 2014>

Set	History
1	mucosa inflammation/ or mucositis/ or stomatitis/ or stomatitis, aphthous/ or stomatitis, herpetic/ or stomatitis/ or aphthous stomatitis/ or aphthous ulcer/ or herpetic stomatitis/ or oral mucositis/ or Mouth Mucosa/ or ((oral or mouth) adj5 mucosa).ti,ab. or (stomatitis or (oral adj5 mucositis) or (aphthous adj5 (stomatitides or ulcer*)) or (canker adj5 sore*) or aphthae or (simplex adj2 oral adj2 herpes) or ((herpet* adj5 gingivostomatitides) or gingivostomatitis) or (herpetic adj5 stomatitides)).ti,ab. or mouth mucosa/ or cheek mucosa/ or gingiva/
2	exp neoplasm/ or exp neoplasms/ or exp antineoplastic agent/ or exp Antineoplastic Agents/ or exp transplantation/ or organ transplantation/ or exp tissue transplantation/ or transplantation, autologous/ or transplantation, heterologous/ or transplantation, heterotopic/ or exp transplantation, homologous/ or exp radiotherapy/ or (neoplasm* or neoplas* or cancer* or oncolog* or tumor* or tumour* or transplant*).mp. or radiation response/ or radiation dosage/ or dose-response relationship, radiation/ or radiotherapy/ or chemoradiotherapy/ or adjuvant chemoradiotherapy/ or radiation response/ or Radiometry/ or Radiotherapy Dosage/ or (((gray or sievert) adj2 unit*) or (radiation adj2 (dosage* or dose or dosing)) or "gy radiation" or "radiation dose-response").mp. or chemoradiotherapy/ or chemoradiotherapy, adjuvant/ or Radiotherapy, Adjuvant/ or radiometry/ or radiation dose/ or rt.fs. or ((adjuvant adj2 chemotherap*) or chemoradiotherap* or radiochemotherap*).mp.
3	(infan* or neonat* or child* or adolescen* or teen* or girl* or boy* or youth* or tot or tots or toddler* or paediatric* or pediatric*).mp.
4	1 and 2 and 3

## REFERENCES

1. Oberoi S, Zamperlini–Netto G, Beyene J, Treister N, Sung L. Effect of prophylactic low level laser therapy on oral mucositis: a systematic review and meta-analysis *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014;**PlosOne (in press)**