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Caphosol Study

A Randomized Controlled Open-Labeled Trial Investigating Topical Caphosol for Prevention of Oral Mucositis in Children, Adolescents and Young Adults Receiving Chemotherapy

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PROTOCOL REVISION HISTORY

Version No.	Revision Date	Summary of Changes	Consent Revised Yes/No
2	02/24/2016	Added updated DSMC language as requested by the MCW DSMC on 1/22/15: This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows: • Review the clinical trial for data integrity and safety. • Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.) • Review all DSM reports. • Submit a summary of any recommendations related to study conduct. • Terminate the study if deemed unsafe for patients. A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary. Any available DSMC letters will be submitted to the IRB of record as required.	YES – Footers/Headers only– updated to protocol v2 Dated 2/24/2016 • Consent • Assent • Consent Spanish Short Form • HIPPA Adult • HIPAA Adult Spanish • HIPAA Child • HIPAA Child Spanish

SYNOPSIS

Study Title: A Randomized Controlled Trial Investigating Topical Caphosol for Prevention of Oral Mucositis in Children, Adolescents and Young Adults (AYA) Receiving Chemotherapy

Randomized Controlled Trial

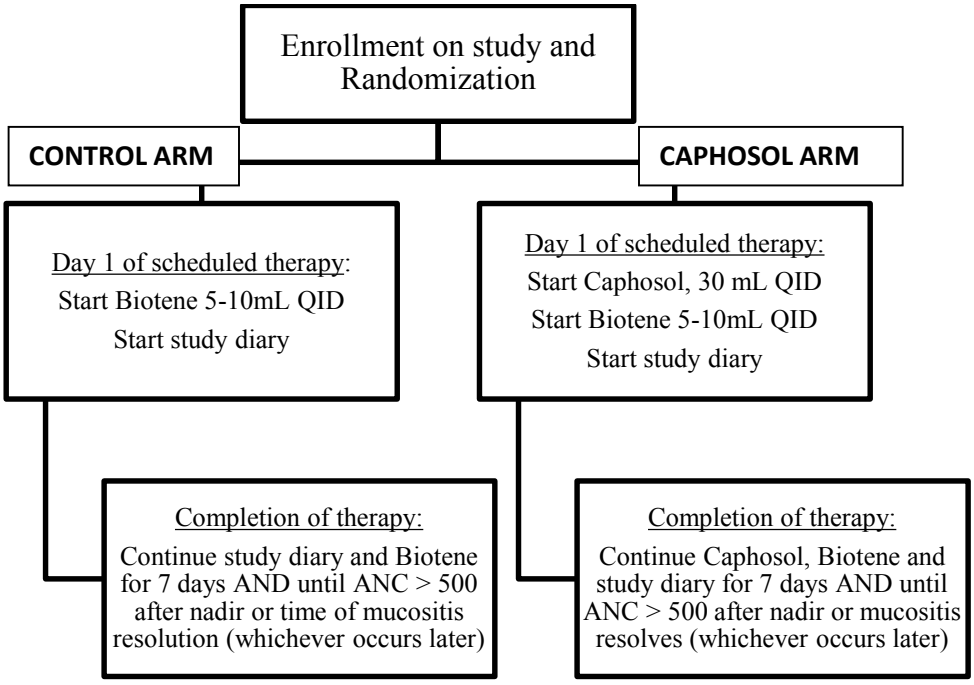
Number of Patients: A total of 96 patients will enroll to this study with 48 patients in the Caphosol group and 48 patients in the control group.

Study Objectives

- **Primary Objectives**
  - To determine if topically administered Caphosol at the initiation of chemotherapy prevents the development of oral mucositis (Grade $\geq$ 2) in children, adolescents and young adults.
  - To determine the tolerability of four times daily Caphosol therapy.

- **Secondary Objectives**
  - To determine if topically administered Caphosol reduces the severity of oral mucositis, as measured by incidence of severe mucositis (CTCAE v4.0 Grades 3 or 4), age-appropriate pain scores (FACES and Likert), use of narcotic pain medicine, number of hospital days and duration of total parenteral nutrition (TPN).

Treatment Plan Schema



Caphosol Administration:

- Take 30 mL QID (can increase frequency up to 6 times daily with symptoms of mucositis).
- Each dose consists of 2, 15 mL syringes, to be mixed at time of administration. Caphosol must be used within 15 minutes of mixing.
- Rinse and gargle (if patient is able) approximately half of the solution (15 mL) for one minute and then spit. Repeat.
- For younger patients (≤ 6 years of age), volume may be reduced to 10-20 mL (5-10 mL x 2).
- For patients unable to successfully rinse and spit, caregivers may paint their mouth (using medical sponge swabs) with the solution x 2. Prior to swabbing the patient's mouth, mix half of the 2, 15 mL syringes into a cup and dip swab prior to coating the inside of the patient's mouth. Repeat
- Patients are to avoid other oral medications, other mouth cares and food or drink for 15 minutes after using Caphosol.
- Take Biotene (5-10 mL) QID swish and spit

Control Arm:

- Take Biotene (5-10 mL) QID swish and spit
- For patients unable to successfully rinse and spit, caregivers may paint their mouth (using medical sponge swabs) with the solution x 2. Prior to swabbing the patient's mouth, mix 5-10 mL into a cup and dip swab prior to coating the inside of the patient's mouth. Repeat

Study Population:

- Oncology patients at any point during their oncology therapy who are at risk of developing oral mucositis defined as:

  Patients receiving one or more of the following chemotherapy agents associated with high incidence of oral mucositis:

  - Actinomycin D
  - Carboplatin
  - Cisplatin
  - Cytarabine at doses $\geq$ 1 gram/m^2
  - Daunorubicin
  - Doxorubicin
  - Methotrexate at doses > 1 gram/m^2
  - Mitoxantrone

- Age 0 to 25 years.
- Voluntary written consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

Exclusion Criteria:

- Patients receiving glutamine therapy for mucositis.
- Patients receiving concurrent Head & Neck radiation therapy or within 6 weeks of completion of radiation therapy.
- Patients receiving autologous or allogeneic hematopoietic cell transplantation
- Pregnant or lactating patients. The agent used in this study is not known to be teratogenic to a fetus, but has not been studied, and there is no information on the excretion of the agent into breast milk. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.
- Known allergy to Caphosol.

Duration of Study: 6-8 months

1.0 BACKGROUND

Mucositis in Children, Adolescents and Young Adults Undergoing Chemotherapy

Oral mucositis, a common and debilitating complication of cancer therapy, is an inflammatory injury to the epithelial and sub-epithelial cells of the oral mucosa. Oral mucositis is thought to develop according to a five-stage model: 1) initiation; 2) up-regulation with generation of messengers; 3) signaling and amplification 4) ulceration with inflammation; and 5) healing, and typically develops 7-14 days into a chemotherapy course (1).

The incidence and severity of oral mucositis depends on many factors including the age and diagnosis of the patient, the specific treatment regimen, underlying oral hygiene and genetic factors (2-4). The incidence of oral mucositis in patients receiving chemotherapy ranges from around 40% of patients receiving myelosuppressive chemotherapy for solid tumors to 70-90% of patients receiving myeloablative therapy prior to stem cell transplant (1, 5, 6). A commonly used grading scale for mucositis is the Common Terminology Criteria for Adverse Events (CTCAE version 4.0) grading scale, where grading is based on both subjective and objective assessments on a 5 point scale (Grade 1 to Grade 5).

Adverse Event	1	2	3	4	5
Mucositis Oral Definition: A disorder characterized by inflammation of the oral mucosal.	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

From the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010) U.S.DEPARTMENT OF HEALTH AND HUMAN SERVICES National Institutes of Health National Cancer Institute, p. 19

Oral mucositis causes significant pain, interferes with eating, talking and swallowing, significantly diminishes enteral nutritional intake and has a substantial negative impact on quality of life (1, 6-10). Patients may require hospitalization for management of the complications of mucositis, including poor nutrition, dehydration and pain (1, 6-10). This becomes a significant burden on the patients, their families and the healthcare system alike. As well injury to the oral mucosa increases the risk of systemic infections (11, 12). Finally, the development of oral mucositis may require delays or dose reductions in future chemotherapy courses, potentially jeopardizing disease cure rates (6, 10).

Despite all that is known about the mechanism, course and complications of oral mucositis, there are no consensus guidelines on prevention or treatment of chemotherapy-induced oral mucositis and there is significant variation on approach to mucositis across treatment centers.

Caphosol (Jazz Pharmaceuticals, Inc. Palo Alto, CA) is a supersaturated aqueous electrolyte solution comprised of sodium phosphate, calcium chloride and sodium chloride, resembling human saliva that was designed in part to replace the normal ionic and pH balance of the oral cavity and been used to prevent and/or treat oral mucositis. Caphosol is hypothesized to diffuse into epithelial intracellular spaces and permeate mucosal lesions in oral mucositis. In addition, calcium may modulate the inflammatory response and tissue repair processes and phosphate may be involved in repairing damage to the mucosal surface. In a 2013 review article by Quinn et al., 24 of the 30 studies reviewed found Caphosol to be beneficial for the prevention and treatment of oral mucositis in patients receiving high-dose chemotherapy and/or radiotherapy (13). The author concluded that despite the heterogeneous nature of the reviewed studies, with many involving small patient numbers, involving single-centers and including historical controls, the data supported strong consideration for the addition of Caphosol to oral mucositis prevention and treatment plans. The largest, randomized study of Caphosol for the prevention and treatment of oral mucositis was a double blind adult study comparing Caphosol to fluoride therapy in 95 allogeneic and autologous hematopoietic stem cell transplant recipients (14). This 2003 study by Papas and colleagues, they reported that 40% of patients in the Caphosol arm had no mucositis compared with 19% in the control arm. Also, patients in the Caphosol arm had significantly fewer mean days of mucositis (3.72 vs. 7.22; p=0.001), duration of pain (2.86 vs. 7.67; p=0.0001), days receiving morphine (1.26 vs. 4.02; p=0.0001), dose of morphine (34.54 mg vs. 122.78 mg; p=0.0001) and days to the onset of neutrophil recovery >200 mm^3 (11.12 vs. 12.56; p=0.00173) (14).

Although a 2014 randomized, controlled trial in 33 pediatric patients receiving high-dose chemotherapy failed to show any therapeutic benefit of Caphosol when initiated at development of mucositis, it did demonstrate safety of Caphosol therapy with no reported side effects (15). This study did not evaluate Caphosol for the prevention of oral mucositis which is the intention of our study. A prevention strategy for development of mucositis was chosen for this study objective as it would potentially allow for less analgesic to be used, less parenteral nutrition and shorter hospital stays compared to a treatment strategy when mucositis has already developed as attempts to enhance recovery of mucositis, particularly in the setting of profound neutropenia, would be more difficult given Caphosol's mechanism of action.

2.0 STUDY OVERVIEW

Eligible patients will be identified in the oncology clinic and/or the oncology ward and consented/enrolled on study. Study patients randomized to the Caphosol arm will begin Caphosol therapy prior to administration of systemic chemotherapy on Day 1 according to protocol. Caphosol administration will continue through the planned chemotherapy administration and until stopping criteria are met. Chemotherapy will be administered either in the MACC Fund Center or the inpatient service. Once the chemotherapy is complete the patient will be discharged to home and followed in the MACC Fund Center at regular intervals as dictated by standards of care. Caphosol treatment will continue at home as outlined in the protocol for 7 days following completion of chemotherapy and adequate neutrophil recovery, or until oral mucositis symptoms resolve, whichever occurs later. In the event the patient requires hospital admission, Caphosol treatment will continue according to protocol. The patient/family will keep a daily drug diary of administration of Caphosol throughout each cycle which will be reviewed by the study team at

each study visit. As well patients in each cohort will record in their diary other oral topical agents they are using and any narcotic and non-narcotic medications used for treatment of pain/mucositis.

2.1 Study Design

This is a randomized controlled trial designed for the purpose of evaluating the efficacy and tolerability of Caphosol therapy for the prevention of oral mucositis (Grade ≥ 2) in children, adolescents and young adults at risk for developing oral mucositis due to their cancer therapy.

Our hypothesis is that by initiating Caphosol at the initiation of chemotherapy administration, we will decrease the incidence and/or severity of oral mucositis (Grade 3 or 4) as well as limit the number of days requiring narcotic analgesics, days of hospitalization and need/duration of total parental nutrition in patients randomized to the treatment group compared to the control group.

Primary Objectives

- To determine if topically administered Caphosol at the initiation of chemotherapy prevents the development of oral mucositis (Grade ≥ 2) in children, adolescents and young adults.

- To determine the tolerability of four times daily Caphosol therapy.

Secondary Objectives

To determine if topically administered Caphosol reduces the severity of oral mucositis, as measured by incidence of severe mucositis (CTCAE v4.0 Grades 3 or 4), age-appropriate pain scores, use of narcotic pain medicine, number of hospital days and number of days on TPN.

3.0 SELECTION OF PATIENTS

Study patients will be recruited from the MACC Fund Center and the oncology inpatient service. Study entry is open to patients regardless of gender or ethnic background. While there will be every effort to seek out and include females and minority patients, the patient population is expected to be no different than that of other oncology studies at the Medical College of Wisconsin.

3.1 Inclusion Criteria

Oncology patients, at initiation of their oncology therapy, who are at risk of developing oral mucositis during their scheduled cancer therapy, defined by meeting one or more of the following criteria:

a. Patients receiving one or more of the following chemotherapy agents:
   - Actinomycin D

- Carboplatin
- Cisplatin
- Cytarabine at doses $\geq$ 1 gram/m^2
- Daunorubicin
- Doxorubicin
- Methotrexate at doses $\geq$ 1 gram/m^2
- Mitoxantrone

b. Age 0 to 25 years
c. Voluntary written consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care

3.2 Exclusion Criteria

a. Patients receiving glutamine treatment for oral mucositis.
b. Patients undergoing autologous or allogeneic hematopoietic cell transplantation are excluded from this study.
c. Patients receiving concurrent Head & Neck radiation therapy or within 6 weeks of completion of radiation therapy.
d. Pregnant or lactating patients. The agent used in this study is not known to be teratogenic to a fetus, but has not been studies, and there is no information on the excretion of the agent into breast milk. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy.
e. Known allergy to Caphosol

4.0 REGISTRATION PROCEDURES

Registration will occur after eligibility is confirmed and the patient/parent has signed the subject consent, but before any treatment has been administered.

The eligibility checklist will be completed at the time of study enrollment.

4.1 Registration

Upon completion of the screening evaluation, eligibility confirmation and obtaining written consent, the patient will be registered in the study file by the Department of Pediatrics Division of Hematology/Oncology/BMT MACC Fund Center Clinical Trials Office (CTO). When the OnCore™ Clinical Trials Management System (CTMS) is fully functioning for this study, the MACC Fund Center CTO will use this program for patient registration.

4.2 Patients Who Do Not Begin Study Treatment

If a patient is registered on the study, and is later found not able to begin the planned study treatment, for whatever reason, the patient will be removed from study and treated at the physician's discretion. Study data will be collected until the time of study removal. The reason for removal from study will be clearly indicated on the case report forms.

If a patient begins treatment, and then decides to come off of study for whatever reason, the patient must be followed per Section 6.1.

4.3 RANDOMIZATION PLAN

The randomization procedure will be based on creating a block for every 4 subjects with 2 subjects of each treatment randomly positioned in the block. Withdrawal is covered in section 5.5. This should provide balance among the two arms for rates of mucositis by disease. If imbalance exists after randomization, covariates will be used for adjustment of the results.

5.0 TREATMENT PLAN

This study is a randomized, controlled trial evaluating the use of topical Caphosol therapy to prevent oral mucositis (Grade $\geq$ 2) in children, adolescents and young adults undergoing chemotherapy. At the time of enrollment, patients will be randomized to either the control arm or the Caphosol arm. The treatment period will extend from the start of chemotherapy and continue for 7 days after completion of chemotherapy AND until the ANC is > 500 after nadir (count recovery) or until the symptoms of oral mucositis resolve; whichever occurs last.

Treatment

Caphosol Arm: Subjects randomized to the **Caphosol Arm** will use Caphosol 4 times per day as follows:

- Each dose consists of two 15 mL syringes, to be mixed at time of administration. Caphosol must be used within 15 minutes of mixing.
    - Subjects may increase the use to 6 times per day if they have symptoms of mucositis.
- Using one of the syringes, rinse and gargle (if patient is able) for one minute and then spit. Repeat using the remaining syringe.
    - For younger patients (less than or equal to 6 years of age), volume may be reduced to two syringes containing 5-10 mL each.
    - For patients unable to successfully rinse and spit, caregivers may paint their mouth (using medical sponge swabs) with the solution two times. Prior to swabbing the patient's mouth, squirt one of the syringes into a cup and using the medical sponge, soak up the solution and use the swab to coat the inside of the patient's mouth. Repeat using the second syringe.
- Patients are to avoid other oral medications, other mouth cares and food or drink for 15 minutes after using Caphosol.

- Patients will also use Biotene (5-10 mL) to swish and spit after the 15 minutes has passed. Biotene is part of our standard of care to prevent oral infections in oncology patients.

Control Arm: Subjects randomized to the **Control Arm** will use Biotene only 4 times per day as follows:

- Use 5 to 10 mL of Biotene to swish and spit
    - For patients unable to successfully rinse and spit, caregivers may paint their mouth (using medical sponge swabs) with the solution two times. Prior to swabbing the patient's mouth, pour Biotene into a cup and using the medical sponge, soak up the solution and use the swab to coat the inside of the patient's mouth. Repeat with a second swab.

The following will be observed:

- Incidence of oral mucositis. Oral mucositis will be defined and characterized by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 as Grade 1-4.
- Severity of oral mucositis, according to:
    - Age-appropriate pain scales (LIKERT and FACES)
    - CTCAE V 4.0 grading
    - Total narcotic usage (both the total amounts in milligrams and the number of days the patient required intravenous narcotic therapy as well as any increase of dose above baseline for patients who are on scheduled chronic use of narcotics)
    - Number of hospital days with oral mucositis present
    - TPN use and duration

The following will be observed on all patients on the Caphosol arm, via the study diary:

- Missed doses of Caphosol and reason
- Side effects attributed to Caphosol therapy
- Use of any other oral topical agents for oral mucositis (dose, schedule, number of doses taken) such as biotene/ chlorhexidine rinses and/or magic mouthwash.
- Use of any non-narcotic pain medications for oral mucositis (dose, schedule, number of doses taken)
- Use of any narcotics for oral mucositis (dose, schedule, number of doses taken)

The following will be observed on all patients on the Biotene arm, via the study diary:

- Use of any other oral topical agents for oral mucositis (dose, schedule, number of doses taken) such as chlorhexidine rinses and/or magic mouthwash.
- Use of any non-narcotic pain medications for oral mucositis (dose, schedule, number of doses taken)
- Use of any narcotics for oral mucositis (dose, schedule, number of doses taken)

5.1 Treatment Plan Schema

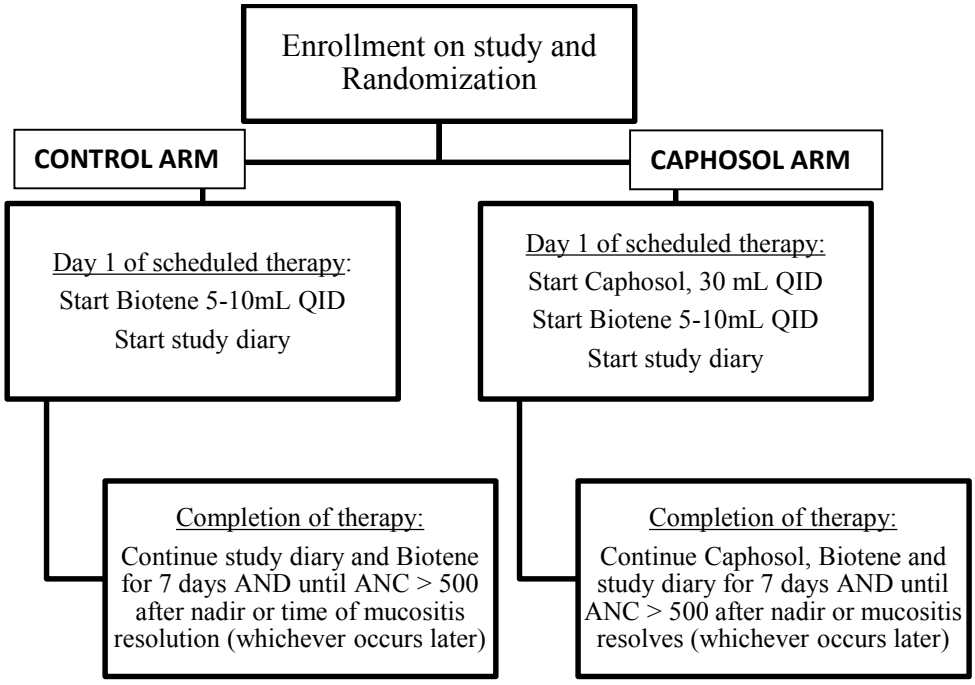


Table 1: Treatment Plan

Day	Agent/Procedure
Enrollment	Randomization to control arm or Caphosol arm
Day 1 of Chemotherapy	Start study diary IF on **Caphosol Arm**: Start Caphosol, 30 mL QID
Completion of Chemotherapy	**Control Arm**: Continue study diary and Biotene for 7 days after therapy completed AND until ANC > 500 after nadir or until mucositis resolution, whichever occurs later. **Caphosol Arm:** Continue Caphosol, Biotene, and study diary for 7 days after therapy completed AND until ANC > 500 after nadir or until resolution of oral mucositis; whichever occurs latest.

5.2 Dose Modifications

The dosing frequency may be increased up to 6 times daily for patients with signs or symptoms of oral mucositis. An increase in frequency of Caphosol administration up to the 6 times daily will not be considered a treatment failure.

If younger patients (< 5 years of age) are unable to tolerate the full volume, the volume may be reduced to a total of 10-20 mL per dose (5-10 mL x 2), as tolerated. For patients unable to swish and spit, caregivers may paint the Caphosol solution (using medical sponge swabs) on the oral mucosa x 2 for each dose.

5.3 Supportive Care Guidelines

Patients on study will receive the standard, recommended supportive cares based on the therapy received.

Allowed oral topical medications on study:

- Standard oral cares, such as scheduled biotene or chlorhexidine rinses
- If needed for symptom management, patients may receive topical viscous lidocaine or topical "magic mouthwash" containing lidocaine, diphenhydramine and Maalox.

5.4 Duration of Therapy

Caphosol will be initiated on Day 1 of scheduled cancer therapy and will continue for:

- 7 days after therapy completion

AND

- ANC > 500 after nadir (count recovery)*

OR

- Resolution of oral mucositis symptom*

*(whichever occurs last)

Caphosol will be continued each time the patient receives chemotherapy where eligibility criteria are met for patients randomized to Caphosol arm.

Caphosol will be discontinued for allergy or patient intolerance. Please see Section 5.6 for criteria for removal from protocol therapy and off study criteria.

5.5 Follow-Up

Study patients will be followed through their first clinic appointment after treatment completion with the appropriate evaluations. Data collection will continue through completion of planned therapy, or until subject meets criteria for removal from protocol therapy or off –study criteria are met as outlined below. Patients who are removed from study per the protocol criteria below, or who withdraw from the study, will not be replaced but will be treated as part of the analysis using either an "intention to treat", "last observation carried forward" or "by imputation of the missing values".

Study evaluations will occur each time chemotherapy is received where Caphosol is administered.

5.6 Criteria for Removal from Protocol Therapy and Off-Study Criteria

5.6.1 Criteria for Removal from Protocol Therapy

- Completion of planned Caphosol therapy (all eligible chemotherapy cycles have been completed)
- Physician determines it is in the patient's best interest
- Adverse Event/Side Effects/Complications which based on the treating physician or patient/family opinion warrant coming off protocol therapy
- Inevaluable
- Patient Intolerance/Refusal

5.6.2 Off-Study Criteria

- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission

6.0 STUDY CALENDAR

Table 2: Required Evaluations*

Evaluations	Pre-Study	Treatment Period
Clinical history	X	Weekly
Physical exam	X	Weekly
Vital exam	X	Weekly
Weight	X	
Height	X	
Performance status	X	Weekly
Oral mucositis grading	X	X
Study diary		Daily
At Each Clinic Visit		
- Oral mucositis grading		X
- Age-appropriate pain scale		X
- Assessment of narcotic use		X
For Patients Requiring Admission		
- Oral mucositis grading		Daily
- Age-appropriate pain scale		Daily
- Assessment of narcotic use		Daily
- Nutrition assessment		Daily

**Patient evaluations (inpatient and outpatient) will occur at least weekly and be collected by the study nurses and entered into the patient's medical record (EPIC) under a separate progress note as well as recorded in the protocol specific electronic case report forms (eCRF) in Oncore.*

7.0 DRUG FORMULATION AND PROCUREMENT

7.1 Caphosol

7.1.1 Other Names

Supersaturated calcium phosphate rinse

7.1.2 Classification

Topical oral agent

7.1.3 Mode of Action

Caphosol is a supersaturated aqueous solution of calcium phosphate and high concentrations of calcium and phosphate ions are hypothesized to diffuse into epithelial intracellular spaces and permeate mucosal lesions in oral mucositis. Caphosol resembles human saliva and is designed to restore the normal ionic and pH balance in the oral cavity. In addition, calcium may modulate the inflammatory response and tissue repair processes and phosphate may be involved in repairing damage to the mucosal surface. There are no known interactions between Caphosol and other drugs. No systemic toxicities have been described when using Caphosol as a mouth rinse.

7.1.4 Storage and Stability

Although commercially available, Caphosol will be considered an investigational product for purposes of this clinical trial. Investigational products are required to be stored in the Investigational Drug service area by central pharmacy in the lower level of the West Tower.

Caphosol is supplied as two separately packaged aqueous solutions; a 15 mL phosphate solution and a 15 mL calcium solution. When mixed, Caphosol solution contains dibasic sodium phosphate 0.032%, monobasic sodium phosphate 0.009%, calcium chloride 0.052% and sodium chloride 0.569% in purified water. Caphosol is stored at room temperature conditions for the duration of its shelf life. It should not be refrigerated.

7.1.5 Dose Specifics

For the purposes of this study, Caphosol will be administered topically at the dose of 30 mL QID. Dose frequency may be increased up to 6 times daily for symptoms of oral mucositis.

If younger patients (age $\leq$ 6 years) are unable to tolerate the full volume, the volume may be reduced to a total of 10-20 mL per dose (5-10 mL x 2), as tolerated. For patients unable to successfully swish and spit, caregivers may paint

the Caphosol solution using medical sponge swabs on the oral mucosa x 2 for each dose.

7.1.6 Administration

Investigational Pharmacy will dispense the agent for this clinical trial and place the unit of use, (oral syringe A & B) in a baggie with label for each dose. Unit dosing the oral syringe A&B in a baggie with med label and date/time due should ensure both A&B being administered.

This process means that the product will be in the patient's med drawer with other meds. If the dosing schedule is 6 doses per day (not 4), then Investigational pharmacy would send the evening and overnight doses with regular meds and bring the AM doses up each morning. Patients who receive Caphosol in the outpatient setting will receive a home supply for 2 weeks with appropriate drug labeling and instructions for use and will be evaluated in clinic for compliance and proper administration of the agent.

Caphosol will be supplied in two 15 mL syringes per dose. These are to be mixed together within 15 minutes of dose administration. Patients are to swish and gargle (if able) one half of the mixture (approximately 15 mL) for one minute, and then spit. Immediately repeat with second half of mixture.

For patients unable to successfully rinse and spit, caregivers may paint their mouth (using medical sponge swabs) with the solution x 2. Prior to swabbing the patient's mouth, mix half of the 2, 15 mL syringes into a cup and dip swab prior to coating the inside of the patient's mouth. Repeat

7.1.7 Side Effects

No side effects are expected. Previous studies have shown Caphosol to be safe and well-tolerated with no known side effects, even when inadvertently swallowed.

Pregnancy: It is not known if Caphosol is teratogenic or passes through breast milk; therefore, pregnant and lactating patients will not be eligible for enrollment on study. Patients who become pregnant while on study receiving Caphosol will become ineligible and removed from protocol therapy.

8.0 ADVERSE EVENT MONITORING, DOCUMENTATION AND REPORTING

Toxicity and adverse events will be classified according to NCI's Common Terminology Criteria for Adverse Events V 4.0 (CTCAE) and reported on the schedule below. A copy of the CTCAE can be downloaded from the CTEP home page:http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

8.1 Definitions

The following definitions are based on the Code of Federal Regulations Title 21 Part 312.32 (21 CFR 312.32(a)).

Adverse Event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Life-Threatening Adverse Event Or Life-Threatening Suspected Adverse Reaction: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death.

Event Attribution Categories: CTCAE does not define an AE as necessarily 'caused by a therapeutic intervention.' The clinical investigator must assign attribution for an adverse event after naming and grading of the event.

Attribution	Description
Unrelated	The AE is clearly NOT related to the intervention
Unlikely	The AE is doubtfully related to the intervention
Possible	The AE may be related to the intervention
Probable	The AE is likely related to the intervention
Definite	The AE is clearly related to the intervention

Unanticipated (unexpected) adverse event or unexpected suspected adverse reaction as defined by the Children's Hospital Wisconsin (CHW) IRB are those that are *not* already described as potential risks in the consent form, *not* listed in the Investigator's Brochure or *not* part of an underlying disease.

Expedited (Rapid) Reporting: Certain events may require rapid notification to entities providing patient safety oversight (e.g. IRB) as detailed in Section 8.3.

	Grade 1	Grade 2		Grade 3		Grade 4 and 5
	Expected or Unexpected	**Expected**	**Unexpected**	**Expected**	**Unexpected**	**Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	Not required	Not Required	**Required**	**Required**
Possible Probable Definite	Not required	Not required	Not Required	Not Required	**Required (Non hematologic only)**	**Required**

8.2 Adverse Event Documentation

Adverse events occurring after the initiation of any study treatment must be documented. There are no expected toxicities from the addition of Caphosol therapy.

Adverse event documentation requirements will be determined based on grade, expectedness and relationship to study therapy as follows:

Stopping Rule Events: The following events count toward a study stopping rule per Section 10.3 and must be reported to the MCW Study Coordinator.

- Any Grade 4 non-hematologic treatment related event
- Any death, regardless of cause during the reporting period for this study from initiation of study treatment to end of study.

Events that count toward an early stopping rule do not necessarily constitute a serious adverse event requiring expedited reporting and should be reported as such only if they meet the criteria for expedited reporting to the IRB as defined in section 8.3.

All patients will be monitored through the treatment period, as it is expected that most treatment related adverse events will occur during this period.

8.3 Adverse Event Reporting Requirements

The reporting period for this study is from initiation of study treatment through completion of Caphosol therapy; however after this time point, the investigator must report upon knowledge any study treatment related event meeting the expedited reporting criteria in the following table.

Regulatory Reports To	Criteria for Reporting	Timeframe	Form to Use	Copy AE To:
CHW IRB	**UPIRSO**: Any event which is unanticipated, involved new or increased risk to subjects, and was at least possibly related to study procedures through Day 60 or the start of a new treatment whichever is earlier	5 calendar days	SAE	MCW SAE Coordinator
	Other problems or events meeting the definition of UPIRSO			
MCW DSMC	Any event that counts toward a study stopping rule.	Within 24 hours of PI notification	SAE	MCW SAE Coordinator
	All unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol.	Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge	SAE	MCW SAE Coordinator

If the SAE meets CHW IRB criteria for expedited reporting, then an official signed report is submitted to the IRB within 5 days. Adverse events which did not meet the CHW Prompt Reporting Criteria as outlined in the CHW IRB policy and procedure should be reported to the IRB at time of continuing review. All deaths, regardless of the cause, need to be reported to the PI within 48 hours and then reported to the IRB.

The Study Coordinator will provide the MCW's Data and Safety Monitoring Committee (DSMC) and CHW IRB with the SAE in an appropriate format depending on the individual SAE (as reported or in a summary format).

9.0 STUDY DATA COLLECTION AND MONITORING

9.1 Data Management

Data management will be performed utilizing an electronic clinical trials management system called OnCore. OnCore is a secure, web-based application designed exclusively to support research protocols

Once an institution consents a patient, they will enter the patient demographics into the OnCore system and assign a study ID. Any paper data (i.e. safety reports, reports generated

from OnCore) will be kept in a locked and secure location within the MACC Fund Center Clinical Trials Office of the Pediatric Hematology/Oncology and Bone Marrow Transplant Program. The Clinical Trials Office has secure, electronic employee badge access only. Any paper data that is generated will be kept for at least 10 years.

9.2 Case Report Forms

Participant data will be collected using protocol specific electronic case report forms (e-CRFs) developed within OnCore based on its library of standardized forms. The e-CRF will be approved by the study Principal Investigator and the Biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the patient into OnCore at time of study entry, completing e-CRFs based on the patient specific calendar, and updating the patient record until the end of required study participation.

9.3 Data and Safety Monitoring Plan (DSMP)

The study's Data and Safety Monitoring Plan will be in compliance with the Medical College of Wisconsin Cancer Center's Data & Safety Monitoring Plan (DSMP).

This study will be reviewed by the Medical College of Wisconsin Cancer Center Data and Safety Monitoring Committee (MCWCC DSMC). A summary of the MCWCC DSMC activities are as follows:
• Review the clinical trial for data integrity and safety.
• Review all unexpected grade 3, and all grade 4, and 5 adverse events, as well as any others requiring expedited reporting as defined in this protocol. (Grades 4 & 5 events must be reported to the DSMC within 5 calendar days of study staff's knowledge.)
• Review all DSM reports.
• Submit a summary of any recommendations related to study conduct.
• Terminate the study if deemed unsafe for patients.

A copy of the MCWCC Data and Safety Monitoring Plan and membership roster will be maintained in the study research file and updated as membership changes. The committee will review reports from the study PI twice annually (or more frequently if needed) and provide recommendations on trial continuation, suspension or termination as necessary.

Any available DSMC letters will be submitted to the IRB of record as required.

For the purposes of data and safety monitoring, this study is classified as moderate risk. Therefore the following requirements will be fulfilled:

- The PI will complete and submit a semi-annual Study Progress Report to the MCW Cancer Center Data and Safety Monitoring Committee (DSMC) with the understanding the MCW DSMC may require more frequent reporting.
- This protocol will be monitored by an individual or group of individuals from the MCW Cancer Center who are not directly or indirectly responsible for the supervision of this trial. Monitoring will occur at a minimum of once per year to ensure all regulatory aspects of this study are in compliance with the FDA and any other

applicable regulatory boards/bodies.

- The PI will oversee the submission of all reportable events per the definition of reportable in Section 8.3 to the MCW Cancer Center's DSMC and the CHW IRB.

9.4 Monitoring

The investigator will permit study-related monitoring, audits, and inspections by the MCW compliance groups. The investigator will make available all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.) will be available for trial related monitoring, audits, or regulatory inspections.

9.5 Record Retention

The investigator will retain study records including source data, copies of case report forms, consent forms, HIPAA authorizations, and all study correspondence in a secured facility for at least 10 years after the study file is closed with the IRB.

In addition, the MACC Fund Center Clinical Trials Office (CTO) will keep a master log of all patients participating in the study with sufficient information to allow retrieval of the medical records for that patient. Please contact the CTO before destroying any study related records.

10.0 STATISTICAL CONSIDERATIONS

10.1 Statistic Endpoints

The study will not stratify based on diagnosis. The effectiveness of the study will be based on comparing incidence and severity of oral mucositis. Safety and tolerance will be based on the differential incidence of severe adverse events. A continuous sequential boundary will be used to terminate the study if the difference in adverse events occurs at a rate of 10% or greater at the interim analysis performed at the end of study month 3. A continuous sequential boundary will also be constructed for a differential rate of 5%.

An interim analysis will be conducted half way through using the O'Brien-Fleming rule for early stopping because of success.

10.2 Statistical Analysis

Comparisons of binary outcomes such as prevention of oral mucositis will use logistic analysis or Fisher's exact test if the numbers are small. Comparisons of the severity of oral mucositis (an ordinal scale) will use the Wilcoxon rank sum test since the data is on a 5 point Likert scale, although there are really only two levels of values. Similarly for the secondary outcome an ordinal pain scale can be treated as an ordinal scale. Length of stay and duration of TPN will use a t-test plus a log transform, if necessary to reduce the skewness of the data. Otherwise the Wilcoxon test will be used.

Although there may be loss to follow-up, we don't expect it because continued

chemotherapy depends on the clearing of the mucositis.

The primary analysis for mucositis will be based on a binary scale (Grade 1 versus Grade ≥2 mucositis) because the mucositis essentially has only two clinically pieces to the scale. It also represents common clinical practice.

10.3 Sample Size Justification

For an alpha of 0.05 and a power of 80%, 48 subjects per group allow detection of a 30% difference in the incidence of oral mucositis (range of oral mucositis is 25% to 50%). Efficacy assessment will occur at study completion.

Twenty subjects per group can detect a 0.6 unit difference in the toxicity scale. This is based on an effect size of 0.90 and a SD of 0.66 units. This is a medium sized clinical difference using Cohen's criteria. This study will serve as a pilot for a larger study. For toxicity, which can only be estimated in the treatment group, 48 subjects in the Caphosol group will allow estimation of a 95% confidence interval of the toxicity of about ± 15%. Assessment of toxicity will occur once the study enrolls 20 patients to each arm to obtain a preliminary estimate (95% CI) for toxicity and again at study completion (to obtain a more precise estimate). While the study is stopped if it passes the sequential boundary, to obtain an estimate of the toxicity and its 95% Confidence interval (95% CI) both an interim analysis and an analysis at the end of the study will be used to estimate the 95% CI – most precisely at the end of the study.

11.0 CONDUCT OF THE STUDY

11.1 Good Clinical Practice

`The study will be conducted in accordance with the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

11.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent, written information given to the patients, safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator.

11.3 Informed Consent

All potential study participants will be given a copy of the CHW IRB-approved consent to review. The investigator or designee will explain all aspects of the study in lay language and answer all questions regarding the study. If the participant (or parents/guardians for a minor) decides to participate in the study, he/she will be asked to sign and date the consent document. Patients who refuse to participate or who withdraw from the study will be treated without prejudice.

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MEDICAL COLLEGE OF WISCONSIN

APPENDIX 1
Eligibility Checklist

INCLUSION CRITERIA

#1 -3 of the following Inclusion Criteria must be marked "Yes" for the patient to enroll on study.

1. **Yes** ☐ **No** ☐ Risk of developing oral mucositis during cancer therapy.
   Patients receiving one or more of the following chemotherapy agents associated with high incidence of oral mucositis (Must check at least one of the following):
   - ☐ Actinomycin D
   - ☐ Carboplatin
   - ☐ Cisplatin
   - ☐ Cytarabine at doses ≥ 1 gram/m^2
   - ☐ Daunorubicin
   - ☐ Doxorubicin
   - ☐ Methotrexate at doses > 1 gram/m^2
   - ☐ Mitoxantrone

2. **Yes** ☐ **No** ☐ Patient Age: Patient is 0 to 25 years of age

3. **Yes** ☐ **No** ☐ Informed Consent: Voluntary written consent obtained before performance of any study-related procedure not part of normal medical care.

EXCLUSION CRITERIA

Each of the following questions must be marked "No" Or "N/A" for the patient to enroll on study

1. **Yes** ☐ **No** ☐ **N/A** ☐ Patient is receiving glutamine therapy for mucositis.

2. **Yes** ☐ **No** ☐ **N/A** ☐ Patient is receiving concurrent Head & Neck radiation therapy or within 6 weeks of completing radiation therapy

3. **Yes** ☐ **No** ☐ **N/A** ☐ Patient is receiving autologous or allogeneic hematopoietic cell transplantation

4. **Yes** ☐ **No** ☐ **N/A** ☐ Female patient who is pregnant or lactating.

5. **Yes** ☐ **No** ☐ **N/A** ☐ Patient has known allergy to Caphosol.

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APPENDIX 2
Performance Status Criteria

For patients 16 years of age and older:

Karnofsky Performance Scale	
Percent	**Description**
100	Normal, no complaints, no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs or symptoms of disease.
70	Cares for self, unable to carry on normal activity or to do active work.
60	Requires occasional assistance, but is able to care for most of his/her needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled, requires special care and assistance.
30	Severely disabled, hospitalization indicated. Death not imminent.
20	Very sick, hospitalization indicated. Death not imminent.
10	Moribund, fatal processes progressing rapidly.
0	Dead

For patients less than 16 years of age:

Lansky Performance Scale	
Lansky Score	**Play Score**
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

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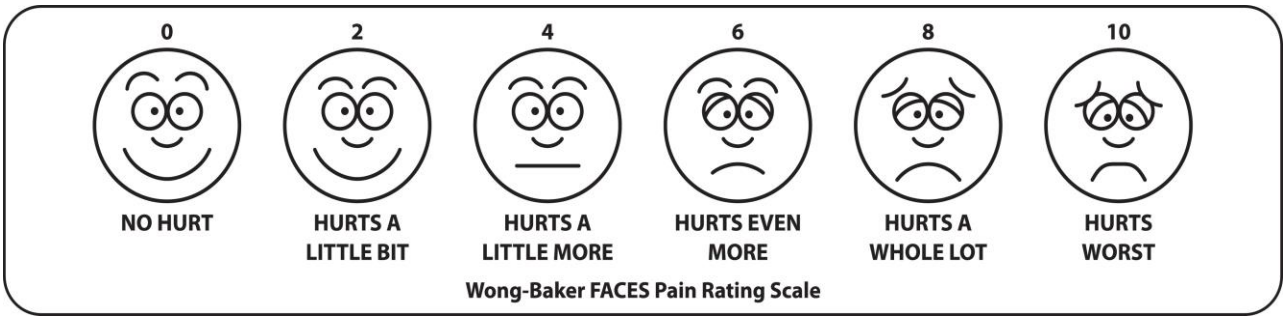
APPENDIX 3
Pain Assessment Scales

Wong-Baker FACES Pain Rating Scale



0 = Very Happy, No Hurt
1 = Hurts Just a Little Bit
2 = Hurts a Little More
3 = Hurts Even More
4 = Hurts a Whole Lot
5 = Hurts as Much as You Can Imagine (Don't have to be crying to feel this much pain)

Explain to the person that each face is for a person who feels happy because he has no pain (no hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you don't have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling.

Pain Rating scale is recommended for subject's age 3 years and older.

Brief Word Instructions: Point to each face using the words to describe the pain intensity. Ask the child to choose face that best describes own pain and record the appropriate number.

Likert 0–10 Numeric Pain Rating Scale