

RADIATION THERAPY ONCOLOGY GROUP

RTOG 98-09

**PHASE III STUDY OF PENTOSANPOLYSULFATE (PPS) IN TREATMENT
OF GI TRACT SEQUELAE OF RADIOTHERAPY**

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SCHEMA

S	<u>Worst Symptom</u>	R	
T	1. Proctitis		PPS
R	2. Diarrhea	A	Two capsules p.o. three times a day
R	3. Radiation-Related Melena		(total 300 mg/day) for two months
A		N	vs.
T	<u>Severity of Symptoms (See Section 11.3)</u>	D	
I	Grade 1		PPS
F	Grade 2	O	Two capsules p.o. three times a day
Y*	Grade 3		(total 600 mg/day) for two months
	<u>Onset of Symptoms Post RT</u>	M	vs.
	1. < 3 months post RT	I	
	2. ≥ 3 months post RT		Placebo
		Z	Two capsules p.o. three times a day
		E	for two months

* Patients with more than one symptom (*e.g., those with proctitis and melena*) will be stratified using the symptom with higher grade severity or (*if both of same grade*) the one which is in investigator's judgement more significant clinically.

Patients may use drugs aimed at relief of radiotherapy-related symptoms along with protocol drugs (*placebo or PPS*). The need for these drugs will be used as one of the criteria for determination of severity (*grade*) of symptoms and for evaluation of the effectiveness of the protocol drugs.

Eligibility: (*See Section 3.0 for details*)

- Patients with Grades 1 to 3 symptoms of radiation related proctitis, diarrhea and/or melena following completion of radiotherapy.
- At least four weeks must have elapsed since the completion of radiotherapy course.
- No bleeding diathesis, peptic ulcers, bleeding ulcers.
- No anticoagulation therapy.
- No concurrent chemotherapy or on any chemotherapy less than a month prior to accession to the study.
- No recent surgery (*less than three weeks prior to randomization*). History of bowel resection makes the patient not eligible.
- Prior or concurrent hormones for prostate cancer are permissible.
- Signed study-specific consent form prior to randomization.

Institution # _____
RTOG 98-09 _____
Case # _____

ELIGIBILITY CHECK (10/26/99)
(page 1 of 2)

- _____(Y) 1. Has the patient received abdominal and/or pelvic radiotherapy?
- _____(Y) 2. Does the patient demonstrate GI-related symptoms of proctitis, diarrhea or melena?
- _____(Y) 3. Is the severity grade (1-3) as specified in Section 11.3 of the protocol?
- _____(N) 4. Can the symptoms be attributed to something other than XRT?
- _____(N) 5. Did the patient's symptoms appear prior to XRT?
- _____(Y) 6. Have at least 4 weeks elapsed since completion of XRT?
- _____(N) 7. Is the patient receiving anticoagulant therapy (*other than aspirin*)?
- _____(N) 8. Does the patient have bleeding ulcers, bleeding diathesis or a peptic ulcer?
- _____(N) 9. Has the patient had any surgery less than 3 weeks prior to today?
- _____(N) 10. Has the patient had a bowel resection?
- _____(Y) 11. Will the patient complete the pretreatment FACE (FA) questionnaire?
- _____(N) 12. Is the patient on chemotherapy or had any chemotherapy in the last month?

The following questions will be asked at Study Registration:

- _____ 1. Institution person randomizing case?
- _____(Y) 2. Has the Eligibility Checklist (*above*) been completed?
- _____(Y) 3. Is the patient eligible for this study?
- _____ 4. Date the study-specific Consent Form was signed? (*must be prior to study entry*)
- _____ 5. Patient's Name
- _____ 6. Verifying Physician
- _____ 7. Patient ID #
- _____ 8. Birthdate
- _____ 9. Race
- _____ 10. Social Security Number

(continued on next page)

Institution # _____

- _____ 11. Gender
- _____ 12. Patient's country of residence?
- _____ 13. Zip Code (9 digit if available)
- _____ 14. Patient's insurance status?
- _____ 15. Will any component of the patient's care be given at a military or VA facility?
- _____ 16. Treatment Start Date
- _____ 17. Study and case numbers if registered to another RTOG protocol.
- _____ 18. Worst Symptom
 - 1. Proctitis
 - 2. Diarrhea
 - 3. Melena
- _____ 19. Severity of Symptoms (See Section 11.3)
 - 1. Grade 1
 - 2. Grade 2
 - 3. Grade 3
- _____ 20. Onset of Symptoms Post RT
 - 1. onset < 3 months post RT
 - 2. onset \geq 3 months post RT
- _____ **Blinded** Treatment Assignment

Completed by _____

Date _____

1.0 INTRODUCTION

- 1.1** The acid mucopolysaccharides (*or glycosaminoglycans*) are high molecular weight linear heteropolysaccharides formed by polymerization of repeating disaccharide units made up of a hexosamine (*glucosamine or galactosamine*) and hexuronic acid (*D-glucuronic or/and L-iduronic acid*) linked by glycosidic bonds. The glycosaminoglycans (*GAG's*) occur in the extracellular amorphous ground substance of all the connective tissues and biological fluids. These macromolecules are present in the tissues as covalently-linked protein-complexes called proteoglycans and as proteoglycan aggregates of very high molecular weights. These are responsible for the physical characteristics of the tissues like shape and compactness. In the biological fluids these macromolecules are present as glycosaminoglycans.
- 1.2** Numerous roles of GAG's have been suggested.¹ These include the control of water and electrolytes in extracellular space, coagulation, wound healing, lubrication of joints and protection of mucosal surfaces, such as those of the urinary and gastrointestinal tract.^{2,3}
- 1.3** The gastrointestinal secretions contain mucins (*consisting of neutral and sulfated glycoproteins and glycosaminoglycans*) secreted by specialized cells located through the gastrointestinal tract. It would appear that the mucus of the GI tract not only provides protection against stresses and auto-digestion but also it is important in healing of the mucosa in disease states.
- 1.4** Treatment related morbidity (*sequelae*) associated with abdominal and pelvic irradiation include nausea and vomiting, diarrhea and proctitis syndrome.⁴ For the purposes of the current discussion diarrhea is defined as frequent loose bowel movements without associated tenesmus. Proctitis syndrome is characterized by tenesmus, frequent bowel movements, mucus and bloody discharge. Diarrhea is quite frequent during abdominal and pelvic irradiation and may persist after completion of treatment or even remain chronic. Proctitis symptoms usually occur during the radiotherapy course and may persist thereafter. They may also occur at any time after completion of treatment. Although proctitis is reversible in the majority of patients, it may show as a protracted course or remain a permanent problem.
- 1.5** It appears reasonable to postulate that most of the sequelae of radiotherapy on the gastrointestinal tract might be related to the disruption of the surface barrier of the bowel. This may be associated with the penetration of the toxic substances into the interstitium and the secondary irritative phenomena. Prompted by the observation that administration of an exogenous GAG, pentosanpolysulfate (*PPS*) resulted in a significant improvement of radiation cystitis syndrome,⁵ a pilot study was conducted at the Washington University School of Medicine in St. Louis, testing the potential value of PPS in the treatment of radiation-related bowel injury. Patients eligible for the study had symptoms of protracted radiation proctitis including tenesmus, mucus and bloody discharge or protracted frequent bowel movements (*diarrhea*) unresponsive to conservative management. Ineligible patients were those with history of bleeding ulcers, bleeding diathesis, recent surgery and also those receiving anticoagulant therapy. The drug PPS was administered at a dose of 150 mg. p.o. t.i.d. In those who did not respond to the initial dose, the dose was increased after two months of treatment, to 300 mg. t.i.d. After 3 months of treatment, PPS was discontinued and the patients were followed at monthly intervals for recurrence of symptoms. In those who did not respond to treatment after three months, the drug was permanently discontinued. In patients who initially responded to PPS and the drug was discontinued, the drug was reinstated for an additional three month period. This procedure (*stopping PPS at 3 months intervals and reinstatement in relapsing patients*) was continued for one year.
- A total of 13 patients were entered on to the study, 11 patients were evaluable. No response was observed in one patient, a partial response seen in another patient, and nine patients (82%) demonstrated a complete response. Following discontinuation of the drug after the first three months of administration, a relapse of symptoms was observed in four of the nine complete responders. All four of these underwent a second course of the drug and all achieved a second complete response.
- Toxicity associated with treatment included a rash that responded to discontinuation of the drug and did not recur after reinstatement of PPS.
- The observed high effectiveness of PPS in the treatment of sequelae of radiotherapy needs to be confirmed in a larger (*phase III*) trial.
- 1.6** The association between sequelae of radiotherapy on the gastrointestinal tract and quality of life are not well documented. Bye et al. examined quality of life during pelvic radiotherapy using the EORTC quality of life questionnaire.⁶ They found low correlation between the side effects queried in the EORTC scale and toxicities. There was also a low correlation between the daily diary card and the EORTC scale.⁶ The

concerns were that the EORTC quality of life questionnaire was not sensitive to sequelae related to pelvic radiation. O'Keefe et al. found that elderly patients with irritable bowel syndrome (IBS) had lower overall quality of life than controls without IBS.⁷ The authors use the Elderly Bowel Symptom Questionnaire (*EBSQ*) and the Medical Outcome Survey (*MOS*).⁷ The *EBSQ* is a 33 item questionnaire that covers abdominal pain, bowel function, and upper gastrointestinal complaints.⁸ The *EBSQ* has been developed as a screening tool and not for repeated assessments in cancer patients. An alternative symptom assessment questionnaire is the Functional Alterations due to Changes in Elimination (*FACE*) developed by Bruner.⁹ *FACE* is an instrument designed to measure the construct of intrusion on daily functioning caused by changes in elimination as measured by two subscales. The two subscales of *FACE* are Changes in Urinary Function (*CUF*) and Changes in Bowel Function (*CBF*). The correlations between *CUF* and the Functional Assessment of Cancer Therapy (*FACT*) range from 0.35 to 0.79.¹⁰

The primary endpoint of this trial is the effectiveness of PPS in the treatment of radiotherapy induced sequelae. A related hypothesis is whether clinical reduction in the severity or cure of the sequelae is meaningful to the patient. *FACE* will be used to determine the patient self-assessment of sequelae and interference in daily activity. The associated hypothesis is whether a clinical reduction in symptoms is associated with a decrease *FACE* score. Since patients have all completed radiotherapy the use of general cancer-specific questionnaires that encompass treatment-related concerns such as *FACT* or the EORTC scale will not be necessary. However, general quality of life effects are a concern. There are two instruments for collecting general quality of life: the Medical Outcomes Survey (*SF-12*) and the Spitzer Quality of Life Index (*SQLI*). The *SF-12* is an abbreviated version of the *SF-36*; The *SF-12* is comprised of two subscales (*mental and physical health*). The *SF-12* has proven reliability and validity and takes only 1-2 minutes to complete.¹¹ The *SQLI* is a five item categorical questionnaire summed in a Likert format with total scores ranging from 0-10. There are no subscale scores for the *SQLI*. The reliability and validity have been established.¹² The *SF-12* and *SQLI* will be applied concurrently with *FACE* prior to the initiation of PPS then at each follow-up for the first two years. Both the *SF-12* and *SQLI* will be used to determine whether PPS impacts overall quality of life and if either correlate with changes in *FACE*. This study should help to determine whether a general, short quality of life instrument is sensitive to changes in symptom status.

3.0 OBJECTIVES

- 3.1 To evaluate the effectiveness of pentosanpolysulfate (*PPS*) in the treatment of the sequelae of abdominal and pelvic irradiation.
- 3.2 To assess the potential toxicity of pentosanpolysulfate or to document the lack of toxicity.
- 3.3 To evaluate the effectiveness of PPS in improving symptoms and quality of life scores.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

- 3.1.1 Patients who received radiotherapy to the abdominal and/or pelvic content and demonstrate radiation related GI symptoms (*proctitis, diarrhea, melena*).
- 3.1.2 A minimum of four weeks must have elapsed since the completion of the radiotherapy course.
- 3.1.3 The severity of symptoms must fit the criteria for grade 1, 2, or 3 (*see Section 11.3*).
- 3.1.4 Patients on hormone therapy for prostate cancer are eligible.
- 3.1.5 Patients must sign a study-specific informed consent form before randomization.

3.2 Ineligibility Criteria

- 3.2.1 Patients with diarrhea, proctitis and/or melena present before initiation of radiotherapy and/or attributed to causes other than radiotherapy.
- 3.2.2 Anticoagulation therapy, bleeding ulcers, bleeding diathesis (*the use of aspirin is acceptable*).
- 3.2.3 Recent surgery (*less than 3 weeks prior to randomization*).
- 3.2.4 Patients on chemotherapy and those who received any chemotherapy less than one month prior to randomization.
- 3.2.5 History of bowel resection.
- 3.2.6 Failure to complete the pretreatment *FACE* questionnaire (*FA*).

4.0 PRE-TREATMENT EVALUATION (10/26/99)

- 4.1 Patient symptoms must be evaluated and scored per Section 11.3.
- 4.2 It is advisable that tests such as endoscopy to assess the pattern of mucosal injury, or stool examination for infectious causes such as *c. difficile* be considered in patients with bowel symptoms with questionable etiology.

- 4.3 Quality of Life questionnaires must be completed before any study drug is administered. Request forms packets from RTOG in advance.
- 4.4 Baseline CBC, PT, and PTT prior to randomization.

5.0 REGISTRATION PROCEDURES

- 5.1 Patients can be registered only after pretreatment evaluation is completed and eligibility criteria are met. Patients are registered prior to any protocol therapy by calling RTOG headquarters at (215) 574-3191, Monday through Friday 8:30 am to 5:00 pm ET. The patient will be registered to a treatment arm and a case number will be assigned and confirmed by mail. The following information must be provided:
- Institution Name & Number
 - Patient's Name & ID Number
 - Verifying Physician's Name
 - Eligibility Criteria Information
 - Stratification Information
 - Demographic Data
 - Study and case numbers if registered to another RTOG study
 - Treatment Start Date

6.0 RADIATION THERAPY

Not applicable to this study.

7.0 DRUG THERAPY

7.1 Description (IND 58,974) (10/26/99)

PPS, sodium pentosanpolysulfate (*SP54, Benechemie, Elmiron®, Pharmacia*), is a semisynthetic sulfated polyanion with heparin-like properties. It has been given orally and intramuscularly in varying doses. Controlled trials by the manufacturer have shown that it reduces thrombogenesis, has fibrinolytic properties, and reduces serum cholesterol and triglyceride levels. Its anticoagulant effect, however, is much less than that of heparin and in fact is confined to its antithrombogenic effect. A review of the literature indicates that its parenteral use is contraindicated in patients with bleeding peptic ulcer (*Reportorio Therapeutica 1976 Ital*) or hemophilic states and hemorrhagic diatheses. The only known potential risks are administration of medication parenterally to patients with history of peptic ulcer and the possibility of allergic reaction to the medication.

7.2 Preparation

PPS and the placebo will be supplied in the oral capsule form. Both PPS and placebo will be coded and administered in a double blind manner.

7.3 Administration (10/26/99)

- 7.3.1 PPS and the placebo will be administered orally on an empty stomach (*one hour before, or two hours after meals*). Patients will take two capsules three times a day for two months. Capsules should be swallowed whole, not crushed or chewed.
- Patients will receive 100 mg of PPS, three times a day, (*total dose 300 mg*) or
 - Patients will receive 200 mg of PPS, three times a day, (*total dose 600 mg*) or
 - Patients will receive placebo, three times a day.
- 7.3.2 If there is no improvement in the patient's symptoms after two months of protocol treatment, the protocol agent will be discontinued. Patients who experience a clinically significant drop in Hgb, Hct, or platelets will discontinue protocol treatment.
- 7.3.3 If the GI symptoms resolve or there is a favorable response (*any reduction in severity grade*) after two months of administration, the protocol agent will be administered for an additional four months for a total of six months.
- 7.3.4 If the GI symptoms relapse after discontinuation of protocol treatment, the drug administration will be resumed for two months; however, there must be a two-week duration of symptoms before resuming protocol treatment.
- 7.3.5 CBC, PT, and PTT will be performed weekly during the first month after randomization.

7.4 Drug Handling and Ordering Procedures

- 7.4.1** The capsules will be provided by Alza Corporation and distributed by Pro-Clinical, Inc. RTOG members must submit the Product Shipping Form (*Appendix IV*) to RTOG at least a week prior to randomizing their first case to the study but after institutional IRB approval has been obtained.
- 7.4.2** After each randomization, RTOG will provide the double-blinded treatment assignment to Pro-Clinical who will ship two cartons (*a two-month supply*) to the randomizing institution by next day shipment (*Priority Overnight*). Study product for randomizations done after 1 p.m. ET will be shipped the following business day. Shipments will be Monday to Thursday only. For example, supplies for a 3 p.m. Thursday randomization will be shipped on Monday (*Tuesday, if Monday is a holiday*).
- 7.4.3** Cartons will be numbered with the patient-specific double-blinded number assigned at randomization. The label will include the drug identification number, the RTOG case number, and the daily amount of drug to be taken. Each carton will contain four blister cards, a one-month supply. Each blister card will last one patient one week, (*7 days plus 1 extra day*). Supplies should be stored at controlled room temperature (*15°-30° C/ 59° -86° F*).
- 7.4.4** The labels will also include the protocol number, packaging lot number, storage requirements and all necessary information required by Federal Regulations.
- 7.4.5** *Study Agent Accountability*
Patients will be issued diaries to record daily doses. The reporting of drug administration will be based upon capsule count. The number dispensed, the number that the patient should have taken during the time period, and the number taken based on the capsule count, will be recorded. Diary-indicated use and the number of capsules the patient should have taken will be compared with the actual remaining capsules. Patients will be asked to bring in their diaries and blister cards. The number of pills dispensed minus the number of pills returned will indicate the number of pills taken. The extra day's capsules should not be taken into account unless they have been taken by the patient to make up for lost or damaged capsules. This number should correspond with the diary; however, any discrepancy should be investigated and reviewed with the patient and ultimately with the principal investigator.
- 7.4.6** After delivery of the initial 2-month supply, additional supplies (*for patients already on-study per Section 7.3.3*) can be obtained by the institution by contacting:

Jackie Nyce
Distribution Projects Coordinator
ProClinical, Inc.
300 Kimberton Road
Phoenixville, PA 19460
(610) 983-4470
FAX (610) 935-4504
8 a.m to 4:30 p.m. ET

- 7.4.7** **All unused product must be destroyed. No supplies will be returned to ProClinical.**

7.5 **Toxicity Reporting**

- 7.5.1** The revised NCI Common Toxicity Criteria Version 2.X will be used to score protocol toxicities. The following guidelines for reporting adverse drug reactions (*ADRs*) apply to any research protocol that uses commercial anticancer agents. The following ADRs experienced by patients accrued to these protocols and attributed to the commercial agent(s) should be reported to the Investigational Drug Branch, Cancer Therapy Evaluation Program, within 10 working days.
- 7.5.1.1** Any ADR which is both serious (*life threatening, fatal*) and unexpected.
- 7.5.1.2** Any increased incidence of a known ADR which has been reported in the package insert or the literature.
- 7.5.1.3** Any death on study if clearly related to the commercial agent(s).
- 7.5.1.4** Acute myeloid leukemia (*AML*). The report must include the time from original diagnosis to development of AML, characterization such as FAB subtype, cytogenetics, etc. and protocol identification.
- 7.5.2** The ADR report should be documented on Form FDA 3500 (*Appendix III*) and mailed to:

Investigational Drug Branch
P.O. Box 30012
Bethesda, Maryland 20824
(301) 230-2330
available 24 hours

7.5.3 *Special Reporting for this Study* (*fax 215/928-0153*)

- 7.5.3.1** All grade ≥ 3 non hematologic toxicities correlated to radiation sequelae under study must be reported to RTOG within 24 hours.

- 7.5.3.2 All grade ≥ 4 hematologic toxicities correlated to radiation sequelae under study must be reported to RTOG within 24 hours.
- 7.5.3.3 Data submission must adhere to the timetable specified by the patient calendar and Section 12.0.

8.0 SURGERY

Not applicable to this study.

9.0 OTHER THERAPY

Patients may use drugs aimed at relief of radiotherapy-related symptoms along with protocol drugs (*placebo or PPS*). The need for these drugs will be one of the criteria for determination of severity grade of symptoms (*see Section 11.0*) and for evaluation of the response to protocol treatment.

10.0 PATHOLOGY

Not applicable to this study.

11.0 PATIENT ASSESSMENTS

11.1 Study Parameters

The specific type (*diarrhea versus proctitis symptoms versus melena*) of the radiotherapy-related morbidity and the severity grade (*See Section 11.3*) will be recorded. Diarrhea is defined as loose, frequent bowel movements without associated tenesmus, considered to be secondary to the effect of radiation on segments of bowel proximal to the rectum. Proctitis is a syndrome characterized by tenesmus, mucus and bloody discharge with or without frequent bowel movements, considered to be secondary to the radiation injury of the rectum. Some patients will present with a combination of both syndromes.

- 11.2 The need for, and the dose of symptom relieving drugs (*Lomotil, Imodium, steroids, opiates, Compazine, etc.*) must be recorded.

- 11.3 The revised NCI Common Toxicity Criteria will be used to assess severity of symptoms:

Grade	Proctitis	Diarrhea	Melena
0	none	none	none
1	increased stool frequency, occasional blood-streaked stools, or rectal discomfort, <u>not requiring medication</u>	increase of < 4 stools/day over pre-treatment	mild without transfusion
2	increased stool frequency, bleeding, mucous discharge, or rectal discomfort, <u>requiring medication</u> ; anal fissure	increase of 4-6 stools/day, or nocturnal stools	---
3	increased stool frequency, requiring parenteral support; rectal bleeding requiring transfusion; or persistent mucus discharge, necessitating pads	increase of ≥ 7 stools/day or incontinence; or need for parenteral support of dehydration	requiring transfusion
4	perforation, bleeding or necrosis or other life-threatening complication requiring surgical intervention (<i>e.g., colostomy</i>)	physiologic consequences requiring intensive care; or hemodynamic collapse	catastrophic bleeding requiring non-elective intervention

- 11.4 The patient's need for symptom-related drugs (*Lomotil, Imodium, steroids, analgesics, narcotics, etc.*) is one of the criteria for determination of the severity grade. In this context, the protocol agents (*PPS or placebo*) are not to be taken into account.

In order to assess the patient's need for the symptom-relieving drugs, they should be tapered or discontinued on a monthly basis.

11.5 Follow Up Schedule (10/26/99)

- 11.5.1 CBC, PT, and PTT will be performed weekly during the first month after randomization.
- 11.5.2 While the symptoms of GI sequelae of radiotherapy persist and the patient is under treatment, the patient will be evaluated monthly. Monthly clinical assessments will include assessments of patient condition, drug tolerance, and response to treatment. Following resolution of the symptoms and therapy is

discontinued, patients will be evaluated every two months for the next six months, then every three months for the next 18 months, then annually until year five. If the symptoms recur and treatment is reinstated then repeat the above evaluation timing. The maximum follow-up is five years from the registration date. Data forms are summaries of the clinical evaluations and are due according to Section 12.1. If deemed clinically appropriate, follow-up evaluations can be carried out by phone or by mail if the patient is unable to come in for an appointment. At each scheduled follow-up, the patient will complete FACE, SQLI, and SF-12 for the first two years (3, 6, 9, 12, 18 and 24 months).

11.5.3 CBC, PT, and PTT will be performed monthly after the first month until treatment is completed.

11.6 Response Criteria

11.6.1 *Complete Response*: absence of symptoms; patients are off all symptom-relieving drugs.

11.6.2 *Partial Response*: reduction in severity grade. In patients with several symptoms (e.g., proctitis/tenesmus and melena), partial response will be determined by assessing the higher grade symptoms. If both are the same grade, partial response will be determined by assessing the symptom which is, in the investigator's judgement, more significant clinically.

12.0 DATA COLLECTION

(RTOG, 1101 Market Street, Philadelphia, PA 19107, FAX#215/928-0153)

12.1 Summary of Data Submission

<u>Item</u>	<u>Due</u>
Demographic Form (A5) Initial Evaluation Form (I1) Baseline Quality of Life Questionnaires (FA, SP, PQ)	Within 2 wks of study entry
Follow-up Form (F1)	Every 3 months from treatment start for 1 year; then q 6 months x 2 years, then annually until 5 years.
Study-Specific Flowsheet (SF)	At 3 months (to include initial 2 months of study agent), at 6 months (if patient receives an additional 4 months of protocol agent), and when additional protocol drug is given.
Follow-up Quality of Life Questionnaires (FC, SD, PF)	At 3, 6, 9, 12, 18, and 24 months from the treatment start date.
Autopsy Report (D3)	As applicable

13.0 STATISTICAL CONSIDERATIONS

13.1 Sample Size

Patients will be randomized among 100 mg of PPS, or 200 mg of PPS, or placebo. When the sample size in each of the three groups is 53, a 0.050 level Chi-square test will have 90% power to detect a difference in proportions characterized by a variance of proportions of 0.016872 and placebo effect of 0.300. **A total of 174 patients will be required** allowing for a 10% ineligibility/inevaluability rate. FACE has a range of 0-60 with a high score indicating greater difficulty with symptoms. When the sample size in each of the 3 treatment groups is 53, a one-way analysis of variance will have 90% power to detect at 0.050 level an effect size of 0.0811. The sample size consideration hold for testing differences between treatment groups for SQLI and SF-12.

13.2 Placebo Response

The placebo response rate will be estimated after 20 patients have been accrued to the placebo arm and evaluated after 3 months. If the placebo rate is substantially different than 30% then the sample size will be reevaluated.

13.3 Accrual

It is expected that five patients per month can be accrued to this study. At that rate this study will complete accrual within 3 years.

13.4 Analyses Plans

13.4.1 Interim Analyses

Interim reports with statistical analyses are prepared every six months until the initial manuscript reporting the treatment results has been submitted. In general, the interim reports will contain information about:

- a) the patient accrual rate with a projected completion date for the accrual phase;
- b) the quality of submitted data with respect to timeliness, completeness, and accuracy;
- c) the frequency and severity of the toxicities.

13.4.2 Interim Analyses of Study Endpoints

There will be two interim analyses of best observed symptom response within 3 months from the start of treatment. At each interim analysis a boundary for rejecting the null hypothesis (H_0) of no difference are set. The following statistic will be used.¹³

$$j_0 (\mathbf{C}\hat{\mathbf{P}}_{j_0})' \left\{ \frac{\hat{P}_0(j_0)(1 - \hat{P}_0(j_0))}{(mj_0)\mathbf{I}} \right\}^{-1} (\mathbf{C}\hat{\mathbf{P}}_{j_0}) / N$$

This is distributed χ^2 . If the value of the test statistic exceed (*larger*) the H_0 boundary of 6.09 then it will be rejected and a recommendation of termination of accrual will be given to the RTOG Data Monitoring Committee (*DMC*).

13.4.3 Analysis For Reporting The Initial Treatment Results

This analysis will be undertaken when each patient has been potentially followed for a minimum of three months. The usual components of this analysis are:

- a) tabulation of all cases entered, and any excluded from the analysis with reasons for the exclusion;
- b) reporting institutional accrual;
- c) distribution of important prognostic baseline variables by treatment arm.
- d) best symptom response reported.
- e) duration of response, evaluated by cumulative incidence.
- f) the FACE, SQLI, SF-12, best response at a time point will be compared at 3 months after the start of treatment to answer the quality of life hypothesis. This comparison will be performed both across and within (*if there is a significant difference in symptom response*) treatment arms. Analysis of variance and mixed effects models will be used.

13.5 Gender and Minority Compliance

	American Indian or Alaskan Native	Asian or Pacific Islander	Black, not of Hispanic Origin	Hispanic	White, not of Hispanic Origin	Other or Unknown	Total
Female	2	2	10	5	34		53
Male	3	3	12	6	97		121
Unknown							
Total	5	5	22	11	131		174

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APPENDIX I

RTOG 98-09

PHASE III STUDY OF PENTOSANPOLYSULFATE (PPS) IN TREATMENT OF GI TRACT SEQUELAE OF RADIOTHERAPY

Sample Patient Consent Form

RESEARCH STUDY

I have the right to know about the procedures that are used in clinical research so I can decide whether to undergo the procedure after knowing the risks, benefits, and alternatives involved. This is an effort to make me better informed so I may give or withhold my consent to participate in clinical research.

PURPOSE OF THE STUDY

It has been explained to me that I have radiation-related bowel symptoms. This study involves the evaluation of a drug named Elmiron, also known as pentosanpolysulfate (PPS). The purpose of this study is to determine whether PPS is effective in treating the side effects of radiotherapy on the bowel. The study will also evaluate the side effects of PPS and if PPS improves my quality of life.

DESCRIPTION OF PROCEDURES (10/26/99)

This study involves at random (*by chance*) assignment to one of three study groups. It is not clear right now which of the three is better. For this reason the group that is to be offered to me will be based upon a method of selection called randomization. Randomization means that my physician will call a statistical office that will assign me to one of the three groups by computer. Neither I nor my physician will know in which of the three groups I am placed. The chance of my receiving one of the three study agents is approximately equal. I will be assigned to either 300 mg of PPS a day or 600 mg of PPS a day or placebo (*inactive or "sugar pill"*). No matter which of these I am assigned to, I will take the capsules the same way.

I will take two capsules three times a day on an empty stomach (*one hour before, or two hours after meals*). I will take them whole and must not crush or chew the capsules.

My doctor will be checking me monthly while I have symptoms and am taking the capsules. If there has been no improvement in my symptoms, I will stop taking the capsules as directed by my doctor. If my symptoms have improved, I will continue to take the capsules for another four months (*total time, six months*). If my symptoms get worse after I stop taking the capsules, my doctor may ask me to start taking them again for two months.

I should not stop taking the capsules until I have checked with my doctor. If I feel as if I must stop, I should notify my doctor. I must return all unused capsules to my doctor at each visit.

The capsules will be provided free of charge by Alza Corporation.

If necessary, my doctor may prescribe medication(s) to relieve my symptoms. These would be taken in addition to the study agents. Any medications my doctor gives me for symptom relief, should be discontinued or reduced periodically to check on my status with the study agents. My doctor will see me monthly as long as I have symptoms. Then I will be seen every two months for six months, then annually. Periodically I will have to complete questionnaires about my symptoms and how I feel.

RISKS AND DISCOMFORTS (10/26/99)

The capsules used in this study may cause all, some, or none of the side effects listed. In addition, there is always the risk of very uncommon or previously unknown side effects occurring.

Experience with PPS in the treatment of radiation-related symptoms is limited. Although the drug seems to be well tolerated, there may be a small risk of bringing on a bleeding tendency. My clotting rate will be measured with a blood test once a

week in the first month. Then my clotting rate will be taken once a month until I stop taking the study capsules. Some patients may have an allergic reaction with rash and itchiness. My physician will be checking me closely to see if there are any side effects from the study agents. This institution is not able to offer financial compensation or to absorb the costs of medical treatment if I am injured by participating in this study.

BENEFITS

It is not possible to predict whether any personal benefit will result from the research program. Possible benefits are relief of my bowel symptoms.

CONTACT PERSONS

(This section must be completed)

For information about my disease and research-related injury, I may contact:

_____	_____
Name	Telephone Number

For information about this study, I may contact:

_____	_____
Name	Telephone Number

For information about my rights as a research subject, I may contact:

(OPRR suggests that this person not be the investigator or anyone else directly involved with the research)

_____	_____
Name	Telephone Number

ALTERNATIVES

Alternatives that could be considered in my case include the use of other medication, as appropriate, or surgery. An additional alternative is no further therapy. My doctor can provide more information about the benefits of the various treatments available. I should feel free to discuss my progress with my doctor. The physician involved in my care will be available to answer any questions I have. I am free to ask my physician any questions concerning this program that I wish both now and in the future.

My physician will explain procedures related to this protocol. Some of these procedures may result in added costs but may be covered by insurance. My doctor will discuss these with me.

VOLUNTARY PARTICIPATION

Participation in this study is voluntary. No compensation for participation will be given. I am free to withdraw my consent to participate in research at any time. Refusal to participate will involve no penalty, or loss of benefits. I am free to seek care from a physician of my choice at any time. If I do not take part in or withdraw from the study, I will continue to receive care.

CONFIDENTIALITY

Records of my progress while on the study will be kept in a confidential form at this institution and in a computer file at the headquarters of the Radiation Therapy Oncology Group (RTOG). The confidentiality of the central computer record is carefully guarded. During their required reviews, representatives of the Food and Drug Administration (FDA), the National Cancer Institute (NCI), qualified representatives of applicable drug manufacturers, and other groups or organizations that have a role in this study may have access to medical records that contain my identity. However, no information by which I can be identified will be released or published unless required by law. Histopathologic material, including tissue and/or slides, may be sent to a central office for review and research investigation associated with this protocol.

I have read all the above, asked questions, received answers concerning areas I did not understand. I willingly give my consent to participate in this program. Upon signing this form I will receive a copy.

Patient Signature *(or Legal Representative)*

Date

APPENDIX II

KARNOFSKY PERFORMANCE SCALE

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 sign or symptoms of disease
70	Cares for self; unable to carry on normal activity or do active work
60	Requires occasional assistance, but is able to care for most personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated, although death not imminent
20	Very sick; hospitalization necessary; active support treatment is necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

APPENDIX III

ADVERSE EVENT REPORTING GUIDELINES

A. GENERAL GUIDELINES

In order to assure prompt and complete reporting of toxicities, the following general guidelines are to be observed. These apply to all RTOG studies and Intergroup Studies in which RTOG participates. **When a protocol toxicity requires more intense, special handling, study-specific reporting procedures supersede the General Guidelines.**

1. The Principal Investigator will report the details of any unusual, significant, fatal or life-threatening protocol treatment reaction to the RTOG Group Chairman and to the Headquarters Data Management Staff (215/574-3214) within 24 hours of discovery. When telephone reporting is required, the Principal Investigator should have all relevant material available. See the protocol-specific criteria to grade the severity of the reaction.
 - a. All deaths during protocol treatment or within 30 days of completion or termination of protocol treatment regardless of cause requires telephone notification within 24 hours of discovery.
2. The Principal Investigator will also report the details of the significant reaction to the Study Chairman by telephone .
3. A written report, including all relevant study forms, containing all relevant clinical information concerning the reported event will be sent to RTOG Headquarters by the Principal Investigator. This must be sent within 10 working days of the discovery of the toxicity unless specified sooner by the protocol (FAX #215/928-0153).
4. The Group Chairman in consultation with the Study Chairman will take appropriate and prompt action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures if this is warranted.
5. For those incidents requiring telephone reporting to the National Cancer Institute (NCI), Investigational Drug Branch (IDB) or Food and Drug Administration (FDA), the Principal Investigator should first call RTOG (as outlined above) unless this will unduly delay the notification process required by the federal agencies.

A copy of all correspondence submitted to NCI, or to another Cooperative Group (in the case of RTOG-coordinated intergroup studies) must also be submitted to RTOG Headquarters when applicable.

6. The Principal Investigator, when participating in RTOG-coordinated Intergroup studies, is obligated to comply with all additional reporting specifications required by an individual study.
7. Institutions must also comply with their individual Institutional Review Board policy with regard to toxicity reporting procedure.
8. Failure to comply with reporting requirements in a timely manner may result in suspension of patient registration.

B. RADIATION TOXICITY GUIDELINES

1. All fatal toxicities (grade 5) resulting from protocol treatment must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
2. All life-threatening (grade 4) toxicities resulting from protocol treatment using non-standard fractionated treatment, brachytherapy, radiopharmaceuticals and radiosurgery must be reported by telephone to the Group Chairman, to RTOG Headquarters Data Management and to the primary Study Chairman within 24 hours of discovery.
3. Appropriate data forms, and if requested a written report, must be submitted to Headquarters within 10 working days of the telephone report.

C. ADVERSE DRUG REACTIONS - DRUG AND BIOLOGICS

An adverse reaction is a toxicity or an undesirable effect usually of severe nature. Specifically, this may include major organ toxicities of the liver, kidneys, cardiovascular system, central nervous system, skin, bone marrow, or anaphylaxis. These undesirable effects may be further classified as "known" or "unknown" toxicities.

Known toxicities are those which have been previously identified as having resulted from administration of the agent. They may be identified in the literature, the protocol, the consent form or noted in the drug insert.

Unknown toxicities are those thought to have resulted from the agent but have not previously been identified as a known side effect.

Commercial and Non-Investigational Agents

- i. Any fatal (*grade 5*) or life threatening (*grade 4*) adverse reaction which is due to or suspected to be the result of a protocol drug must be reported to the Group Chairman or to RTOG Headquarters' Data Management Staff and to the Study Chairman by telephone within 24 hours of discovery. Known grade 4 hematologic toxicities need not be reported by telephone.
- ii. Unknown adverse reactions (\geq *grade 2*) resulting from commercial drugs prescribed in an RTOG protocol are to be reported to the Group Chairman or RTOG Headquarters' Data Management, to the Study Chairman and to the IDB within 10 working days of discovery. FDA Form 3500 is to be used in reporting details. All relevant data forms must accompany the RTOG copy of Form 3500.
- iii. All neurotoxicities (\geq *grade 3*) from radiosensitizer or protector drugs are to be reported within 24 hours by phone to RTOG Headquarters and to the Study Chairman.
- iv. All relevant data forms must be submitted to RTOG Headquarters within 10 working days on all reactions requiring telephone reporting. A special written report may be required.

Reactions definitely thought not to be treatment related should not be reported, however, a report should be made of applicable effects if there is a reasonable suspicion that the effect is due to protocol treatment.

Investigational Agents

Prompt reporting of adverse reactions in patients treated with investigational agents is mandatory. Adverse reactions from NCI sponsored drugs are reported to:

Investigational Drug Branch (*IDB*)
P. O. Box 30012
Bethesda, MD 20824
Telephone number available 24 hours
(301) 230-2330 FAX # 301-230-0159

i. Phase I Studies Utilizing Investigational Agents

- | | |
|--|--|
| - All deaths during therapy with the agent. | Report by phone within 24 hours to IDB and RTOG Headquarters.
**A written report to follow within 10 working days. |
| - All deaths within 30 days of termination of the agent. | As above |

- All life threatening (*grade 4*) events which may be due to agent. As above
 - First occurrence of any toxicity (*regardless of grade*). Report by **phone within 24 hours** to IDB drug monitor and RTOG Headquarters. ****A written report may be required.**
- ii. *Phase II, III Studies Utilizing Investigational Agents*
- All fatal (*grade 5*) and life threatening (*grade 4*) known adverse reactions due to investigational agent. Report **by phone** to RTOG Headquarters and the Study Chairman within 24 hours ****A written report must be sent to RTOG within 10 working days with a copy to IDB. (*Grade 4 myelosuppression not reported to IDB*)**
 - All fatal (*grade 5*) and life threatening (*grade 4*) unknown adverse reactions resulting from or suspected to be related to investigational agent. Report **by phone** to RTOG Headquarters, the Study Chairman and IDB within **24 hours**. ****A written report to follow within 10 working days.**
 - All grade 2, 3 unknown adverse reactions resulting from or suspected to be related to investigational agent. ****Report in writing** to RTOG Headquarters and IDB within 10 working days.

**** See attached (*if applicable to this study*) NCI Adverse Drug Reaction Reporting Form**

APPENDIX IV

STUDY PRODUCT SHIPPING FORM

RTOG 98-09

PPS vs. Placebo

Study product will be mailed only to institutions who have identified a single individual for receipt of shipment. This form must be completed and returned to RTOG Headquarters prior to registering any patient on study. Documentation of IRB approval must be enclosed. Allow adequate processing time (*7-10 days*) at Headquarters before calling to register your first patient.

SHIP TO:

Name: _____

Address: _____

(No P.O. Box Numbers)

Telephone: _____

Fax#: _____

RTOG Institution#: _____

Institution Name: _____

IRB Approval Date: _____

(attach copies of IRB approval and sample consent form)

Investigator (*PI*) Signature _____ Date: _____

Investigator Name (*Print*) _____

Investigator NCI # (*Required*) _____

Return to:

*RTOG Headquarters
1101 Market Street
Philadelphia, PA 19107*

**ATTN: ELAINE PAKURIS
FAX# 215/574-0300**

RTOG Headquarters Approval _____ Date: _____