PROTOCOL COVER PAGE

Protocol

A Randomized, Non-Inferiority Study of a Hydrogel Packing System Compared to Standard of Care Packing During Image-Guided High-Dose Rate Brachytherapy Boost for Cervical Cancer

Version Date: 16 November 2021

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Protocol Number: RadOnc 003

Principal Investigator: Kara Romano, MD

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the NIH/NCI Terms and Conditions of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the overall Principal Investigator, and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

Lead Principal Investigator		
_____	_____	_____
Name (print)	**Signature**	**Date**
Site Principal Investigator		
_____	_____	_____
Name (print)	**Signature**	**Date**

ABBREVIATIONS

AE	Adverse Event
AHN	Allegheny Health Network
aVAE	Acute Vaginal Adverse Events
CC DSMC	Cancer Center Data Safety Monitoring Committee
CFR	Code of Federal Regulations
CET	California Endocurietherapy
COC	Certificate of Confidentiality
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
D2cc	Dose to the Hottest 2 cc (for each organ)
EBRT	External Beam Radiation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Forms
EDC	Electronic Document Capture
EMBRACE	Image guided intensity modulated **E**xternal beam radiochemotherapy and **M**RI based adaptive **BRA**chytherapy in locally advanced **CE**rvical cancer
GCP	Good Clinical Practice
HDR	High-Dose Rate
HIPAA	Health Insurance Portability and Accountability Act
HRT	Hormone Replacement Therapy
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
IRB-HSR	Institutional Review Board for Health Sciences Research
IUD	Intrauterine Device
kPA	Kilopascal
KPS	Karnofsky Performance Status
MRN	Medical Record Number
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIH	National Institutes of Health
NIH IC	NIH Institute or Center
NSR	Non-Significant Risk
OHRP	Office for Human Research Protections
PEG	Polyethylene glycol
PEGDA	Polyethylene glycol diacrylate
PRC	Protocol Review Committee
PI	Principal Investigator
QC	Quality Control
RT	Radiation Therapy
SAE	Serious Adverse Event
SOA	Schedule of Activities
SOP	Standard Operating Procedure
SPRT	Sequential Probability Ratio Test
UADE	Unanticipated Adverse Device Effect
UP	Unanticipated Problem
US	United States
UVA	University of Virginia
UVA CC	University of Virginia Coordinating Center
VBP	Vaginal Balloon Packing
VGP	Vaginal Gauze Packing
VHPS	Vaginal Hydrogel Packing System
WOCBP	Women of Childbearing Potential

PROTOCOL SUMMARY

1.1 Synopsis

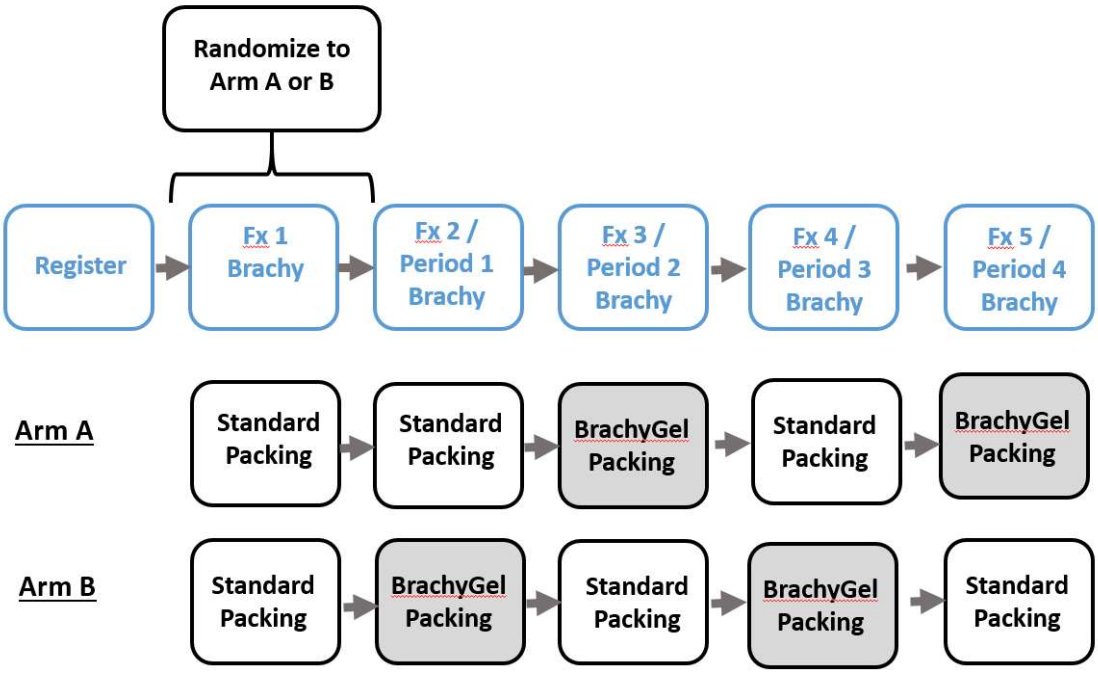
Title:	A Randomized, Non-Inferiority Study of a Hydrogel Packing System Compared to Standard of Care Packing During Image-Guided High-Dose Rate Brachytherapy Boost for Cervical Cancer
Study Description:	Brachytherapy is administered in conjunction with external beam radiation therapy and concurrent chemotherapy in women with locally advanced cervical cancer and is an essential component of curative therapy for this disease.[1] Contemporary high-dose rate (HDR) brachytherapy is commonly delivered in 4-6 separate fractions on an outpatient basis with conscious sedation or mild oral sedation. Vaginal packing is a mandatory component of cervical cancer brachytherapy,[1] serving to displace the rectum and bladder from the high-dose regions and to stabilize brachytherapy applicators (*Figure 2*). Traditional vaginal packing methods include vaginal gauze packing (VGP) and rectal retractors (also called posterior vaginal speculum blades or rectal blades). VGP has been the preferred packing method in most centers due to its availability and low cost, but it causes patient discomfort and lacks reproducibility since it is highly dependent upon physician placement.[2] Rectal retractors provide some displacement of the rectum but do not displace the bladder. Additionally, they are difficult to place due to device crowding from the vertical column of applicators and rectal retractor. Vaginal balloon packing (VBP) methods have been developed to provide a more comfortable and reproducible method of vaginal packing, but these are expensive.[2-7] The high cost limits uptake of VBP in the US, since hospitals must absorb this cost for a treatment that already delivers relatively poor reimbursement compared to other radiation modalities.[8] Current packing options are suboptimal for contemporary image-guided brachytherapy delivered on an outpatient basis under mild sedation. This study validates the clinical performance of a new hydrogel-based packing technique (BrachyGel Vaginal Hydrogel Packing System, (BrachyGel VHPS)) in patients with cervical cancer. This approach is expected to meet the needs of contemporary, image-guided brachytherapy at a low cost and with much less patient discomfort. Participants will receive brachytherapy according to standard guidelines but packing would alternate between standard and BrachyGel. Participants will assess discomfort/pain, and clinicians and physicists will assess imaging properties, completeness and overall experience. BrachyGel VHPS is considered by the FDA to be a non-significant risk (NSR) device and therefore this study does not require an Investigational Device Exemption (IDE) from the FDA.
Objectives & Endpoints:	

	<table><tr><th>Objectives</th><th>Endpoints</th></tr><tr><td>Primary</td><td></td></tr><tr><td>To determine if BrachyGel Vaginal Hydrogel Packing System (BrachyGel) is non-inferior to standard method vaginal packing (standard) in dose thresholds for the rectum and the bladder.</td><td>The dose to the hottest 2 cc (D2cc) (in Gy) for the rectum and the bladder in periods 1 and 2 (e.g. fractions 2 and 3).</td></tr><tr><td>Secondary</td><td></td></tr><tr><td>To estimate the difference in the safety profile of BrachyGel compared to standard vaginal packing.</td><td>Frequency, intensity, and duration of adverse events in periods 1 through 4 (e.g. fractions 2 through 5).</td></tr><tr><td>To estimate period effects in dosimetry thresholds (D0.1cc, D1cc, D2cc) between BrachyGel and standard vaginal packing for the rectum and the bladder.</td><td>The dose to the hottest 0.1 cc (D0.1cc), 1 cc (D1cc), and 2 cc (D2cc) (in Gy) for the rectum and the bladder in periods 1 through 4 (e.g. fractions 2 through 5).</td></tr><tr><td>Exploratory</td><td></td></tr><tr><td>To estimate the difference in participant-reported discomfort between BrachyGel and standard vaginal packing</td><td>Participant-reported discomfort from packing scored on a 4 point scale for periods 1 through 4 (e.g. fractions 2 through 5).</td></tr><tr><td>To estimate the difference in physician/physicist evaluation of imaging properties and completeness of packing between BrachyGel and standard vaginal packing.</td><td>Physician/physicist evaluation of imaging properties and completeness of packing scored on a 4 point scale for periods 1 through 4 (e.g. fractions 2 through 5).</td></tr><tr><td>To estimate the difference in physician-scored use experience between BrachyGel and standard vaginal packing.</td><td>Physician-scored use experience scored on a 4-point scale for periods 1 through 4 (e.g. fractions 2 through 5).</td></tr></table>
Study Population:	Adult women with locally advanced cervical cancer (FIGO Stages IB1-IVB) for whom brachytherapy boost is planned using intracavitary high-dose rate brachytherapy as part of definitive radiation therapy.
Description of Sites/Facilities Enrolling Participants:	Participants will be enrolled at the University of Virginia and at the Allegheny Health Network
Description of Study Intervention:	Participants will receive brachytherapy according to clinical care and will alternate between standard packing and BrachyGel packing. The order of alternation will vary between Arms A and B.
Study Duration:	Accrual should be completed within 14 months and data collection and analysis will take after 12 additional months (total of 26 months).

Participant Duration:	Each participant will receive 5 fractions of brachytherapy, each about 2-7 days apart, followed by a 30 day safety visit.

1.2 Schema

Figure 1. Study Schema



2 INTRODUCTION

2.1 Study Rationale

Brachytherapy, an essential component of multidisciplinary cancer care, is increasingly image-based and focused on a customized, three-dimensional treatment plan.[9] For women with locally advanced cervical cancer, the most common cancer among women worldwide, brachytherapy is administered in conjunction with external beam radiation therapy and concurrent chemotherapy.[1] and it is an essential component of curative therapy in this patient population. Technological advances have ushered in a new era of elegant, highly conformal, image-based

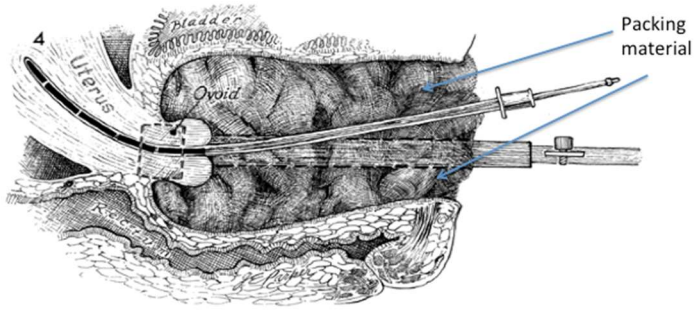


Figure 2. Tandem and Ovoid Brachytherapy with Intrauterine Tandem and Ovoids and Vaginal Gauze Packing

treatment with high dose-rate (HDR) intra-cavitary brachytherapy with tandem-based applicators. Contemporary HDR tandem-based brachytherapy is commonly delivered in 4-6 separate fractions on an outpatient basis with conscious sedation or mild oral sedation, as opposed to traditional low dose-rate brachytherapy delivered in 1-2 insertions with general anesthesia.

Vaginal packing is a mandatory component of cervical cancer brachytherapy,[1] serving to displace rectum and bladder from the high-dose regions and to stabilize brachytherapy applicators (*Figure 2*). Traditional vaginal packing methods include vaginal gauze packing (VGP) and rectal retractors. These options, however, are suboptimal for contemporary image-guided brachytherapy delivered on an outpatient basis under mild sedation. Although VGP is the preferred packing method in most centers because of its availability and low cost, it causes patient discomfort in the modern era of outpatient, multi-fraction HDR brachytherapy courses and lacks reproducibility because it is highly dependent upon physician placement.[2] Placement of VGP has been cited as the most technique-dependent part of the entire cervical cancer brachytherapy procedure [7]. Rectal retractors, also known as posterior vaginal speculum blades or rectal blades, do provide some displacement of the rectum, but do not displace the bladder. Additionally, they are difficult to place due to device crowding from the vertical column of applicators and rectal retractor.

Vaginal balloon packing (VBP) methods have been developed to provide a more comfortable and reproducible method of vaginal packing.[2-7] However, in the US commercially available VBP (Alatus, RadiaDyne, LLC, Houston, TX) costs approximately $400 per application, totaling $2,000 for a 5-fraction course. High cost limits uptake of VBP in the US, since hospitals must absorb this cost for a treatment that already delivers relatively poor reimbursement compared to other radiation modalities.[8]

Recently, a new hydrogel-based packing system has been developed: BrachyGel Vaginal Hydrogel Packing System. On the basis of the results from the pre-clinical testing, the BrachyGel Vaginal Hydrogel Packing System should improve comfort for patients and should be easier for physicians to utilize during brachytherapy. Additionally, it is expected to reduce variation in physician performance, better pack lateral and irregular regions of the vagina (*Figure 4*), image clearly by CT and MRI, minimize air pockets (*Figure 3*), and provide a more affordable option compared to the commercial balloon product.

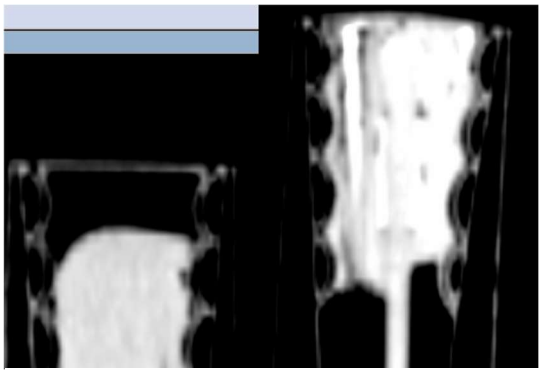


Figure 4. BrachyGel (right) expands to fill irregular cavities within a phantom, in contrast to the fixed shape of VBP (left).

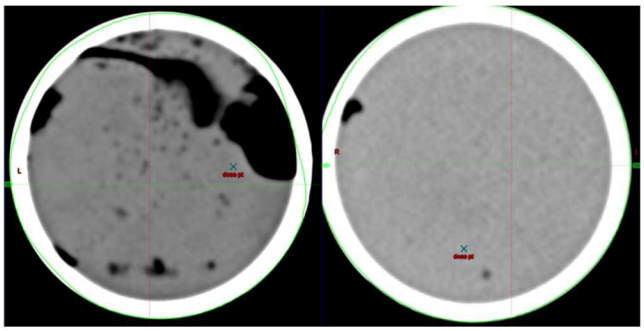


Figure 3. BrachyGel (right) provides uniform filling, in contrast to gauze (left). Both materials shown in glass jars of uniform diameter. The blue X represents a dose point as used in brachytherapy planning software.

2.2 Background

2.2.1 Cervical Cancer and Brachytherapy

In 2016, there were an estimated 12,990 new diagnoses of cervical cancer and 60,050 diagnoses of uterine cancer in the United States.[10] Brachytherapy is standard of care treatment for the majority of these women, approximately 8,000 women with cervical cancer and 42,000 women with uterine cancer. Based on the average number of procedures per patient (5 for cervical, 3 for uterine), we project over 150,000 individual brachytherapy procedures in the US alone. The polymer hydrogel solution (BrachyGel) provides a tailored solution that fits ideally within an image-based brachytherapy paradigm. The past two decades have seen an overall trend toward increasing implementation of image-based brachytherapy techniques with volume-based prescriptions and advanced treatment planning using CT and MRI[11,12]. This product is tailored for image-based brachytherapy, providing customized packing that is visualized well on CT and MRI.

2.2.2 Standard of Care Packing Options

Table 1. Existing vaginal packing options for use with tandem-based cervical cancer brachytherapy.

Vaginal Packing Strategy	Strengths	Limitations
Gauze	-Inexpensive -Amount of gauze and specific placement controlled by physician -Displaces bladder and rectum	-Uncomfortable for patient -Limited use for outpatients, was developed in era of inpatient brachytherapy -Heterogeneous density -Prolonged insertion process involving manual packing of gauze strip with forceps
Balloon Packing Device (i.e., Alatus system by Radiadyne in Houston, TX)	-Rapid insertion of 2 balloons -Can be inflated with dilute contrast, improving image and providing attenuation -Displaces bladder and rectum, may improve dosimetry vs gauze[5,6]	-Exceedingly expensive (~$400 per fraction for a total of $~2000 per 5-fraction course) -Device crowding in vaginal space due to 3 brachytherapy devices and 2 balloons with tubing -Heterogeneous density -Interference of posterior balloon with posterior edge of most common tandem applicator (Fletcher-Suit), which curves to contact posterior vaginal wall
Rectal Retractor	-Provides some displacement of rectum	-Difficult to place due to device crowding from vertical column of applicators and rectal retractor -Heterogeneous density -Does not displace the bladder

2.2.3 BrachyGel Vaginal Hydrogel Packing System

The product consists of the hydrogel solution, delivery gun, and a reaction bag. After standard brachytherapy applicators are in place, one reaction bag is inserted into the anterior vagina and a second bag into the posterior vagina. The hydrogel reagent containers are then placed within the delivery gun and connected to the reaction bag tube. The hydrogel reagents mix within the reaction bag (including the tubing) and the hydrogel

expands within the bag to serve as vaginal packing. The expansion of the hydrogel serves to displace tissue and conform to the patient anatomy to fill the vaginal space. The posterior and anterior reaction bags are filled separately. *Figure 6* shows the anticipated steps involved in clinical use of the **BrachyGel Vaginal Hydrogel Packing System.** The series of steps shown is similar to those involved in VBP, so the time required for placement of the BrachyGel packing should be similar to the time required for placement of the Alatus balloon system or the VGP system. However, unlike VGP, placement of the BrachyGel packing does not require forceps to insert strips of gauze in the vagina. Thus, the Brachygel packing approach should improve comfort for patients and be easier for physicians to place.

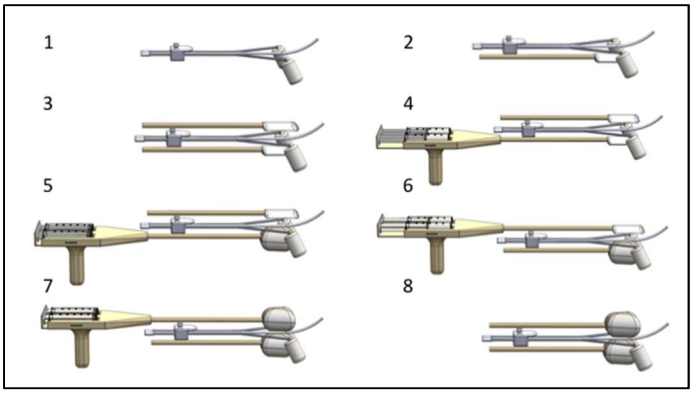


Figure 6. The deployment of the BrachyGel Vaginal Hydrogel Packing System shown in 8 steps to provide posterior and anterior packing. Vaginal packing is the last part of the implant procedure.

With the BrachyGel VHPS, the thiol-Michael addition reaction leads to hydrogel formation and expansion *in situ* within the vaginal cavity, providing a ~10 kPa force to displace vaginal tissue (chosen to approximate pressure from the Valsalva maneuver[13]) *and conforming to a range of cavity shapes and dimensions* (*Figure 5*). The expansion to fill the vaginal cavity occurs with minimal air pockets, which is an improvement over the other available packing methods. The hydrogel surrounds the applicator and conforms to the vaginal cavity, allowing for a fixed-geometry, reusable applicator to serve any size or shape cavity. The imaging characteristics (*Figure 2)* on CT and MRI are ideal for use as vaginal packing during pelvic brachytherapy, with a homogeneous appearance that helps discern packing from adjacent bladder and rectum. This is the first use of a hydrogel technology to provide customized filling of a body cavity during radiation therapy. Furthermore,

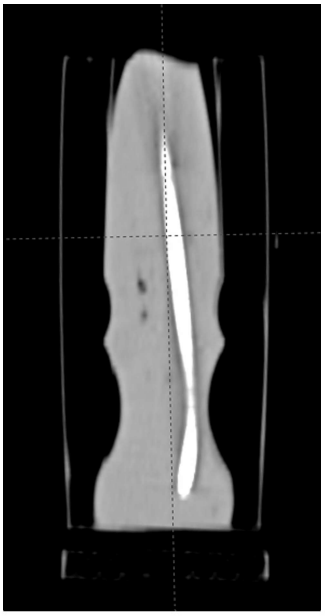


Figure 5. Expansion of hydrogel to conform to shape of cylindrical phantom designed to have varied diameter.

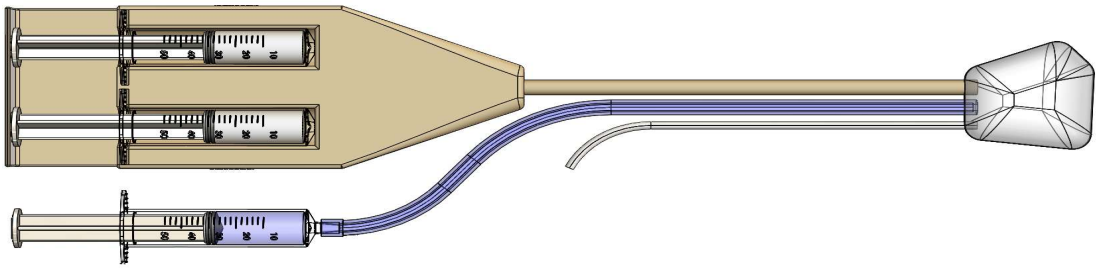


Figure 7. Hydrogel delivery system design, include injection of hydrogel reagents into bag for reaction inside the bag, port to introduce saline, and air vent to release air from the bag during reaction.

it meets a need for a customized packing that readily conforms to any anatomical variation. This improves upon the VBP method, which offers only a range of filling of a pre-set shape and volume.

The delivery system design also contains innovative characteristics that are not available in current packing systems (*Figure 7*). The BrachyGel system includes a vent tube for air to escape from the bag while the hydrogel forms. In addition, there is a tube available for the physician to inject saline prior to removing the hydrogel packing in cases where a softer hydrogel would help with extraction of the packing. These design characteristics optimize the imaging characteristics of the packing (by evacuating air), allow fine-tuning by the physician (saline port), and maximize patient comfort.

2.2.4 Pre-Clinical Experience

The BrachyGel Vaginal Hydrogel was formulated on the basis of the attributes of the thiol-Michael addition reaction (*Figure 9*), which is unprecedented as a method for customized vaginal packing. This approach is based upon its biocompatibility, limited production of heat, and favorable imaging and radiation attenuation properties of constituent materials. The thiol-Michael click reaction involves the base or nucleophile-catalyzed addition of a thiolate into an electron-deficient alkene. The reaction was chosen due to the ability to produce a biocompatible gel that forms quickly and reliably. Among its many other uses, the thiol-Michael addition reaction finds significant application in hydrogel synthesis with precursors including poly(ethylene glycol) (PEG)-based materials, polysaccharides, polypeptides, and synthetic materials. Common applications include drug-delivery, tissue engineering, and tissue repair. The development of this hydrogel packing strategy is described in a 2017 article in *Polymer.*[14]

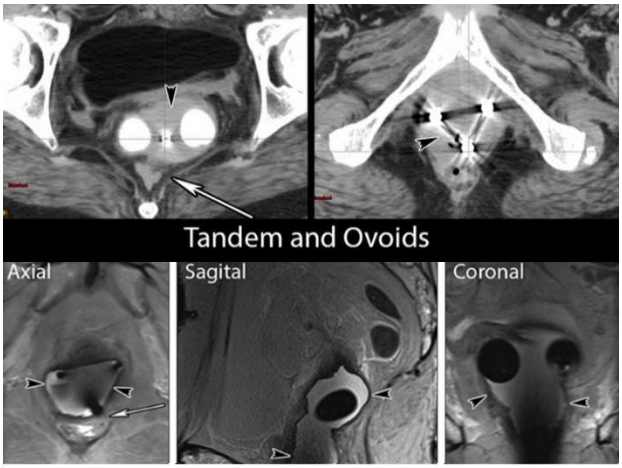


Figure 8. CT (above) and MRI (below) images of hydrogel packing applied to cadaver with tandem and ovoid applicator in place. There is homogenous hydrogel signal (black arrows) with rectum displacement (white arrows).

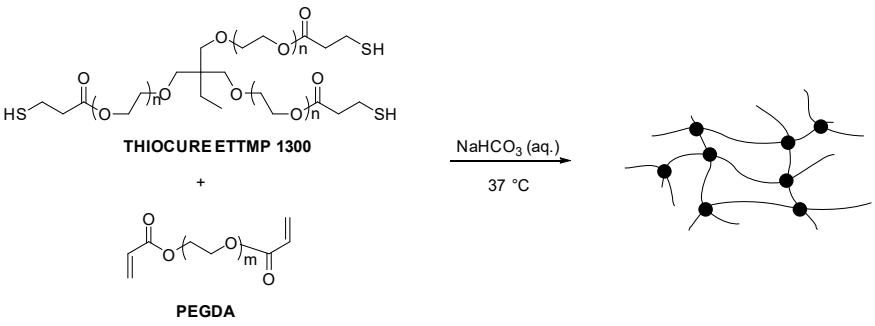


Figure 9. Approach to form hydrogel using an aqueous solution of trifunctional thiol THIOCURE ETTMP 1300 and poly(ethylene glycol) diacrylate (PEGDA).

The suitability of a PEG-based hydrogel for the intended use as vaginal packing has been demonstrated. A mild base ($NaHCO_3$) rapidly formed a hydrogel *in vitro* using this reaction. Characteristics included rapid hydrogel-formation in less than 2 minutes, a hydrogel modulus capable of displacing vaginal tissue (~10 kPa) with a lack of appreciable soluble species after the reaction, and the ability to absorb additional water after hydrogel formation. Measuring the effect of formulation variables such as PEGDA molecular weight, initial polymer concentration, and base concentration on the hydrogel-formation rate and modulus demonstrated hydrogel properties well suited for brachytherapy packing materials. The water absorption of the hydrogel revealed its ability to absorb water in order to fine-tune tissue displacement. CT and MRI imaging studies displayed favorable radiation attenuation, demonstrating clear hydrogel distinguishability from native tissue and the metal applicator, vital for image-guided treatment planning (*Figure 8*). Biological evaluation against human vaginal epithelial cells verified hydrogel cytocompatibility. Based on available public information, this constitutes the first use of a water-absorbing hydrogel designed as a packing solution for pelvic brachytherapy applications.

2.2.5 Relevant Clinical Experience

The investigational product has been used in cadavers, but not in living humans. Data related to cadaver studies, biocompatibility and leakage studies may be found in the investigator's brochure.

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

Vaginal brachytherapy is associated with the following acute side effects according to the EMBRACE study (Image guided intensity modulated **E**xternal beam radiochemotherapy and **M**RI based adaptive **BRA**chytherapy in locally advanced **CE**rvical cancer).

In a study of over 1000 patients receiving brachytherapy, urinary morbidity, in particular urinary frequency, urgency, incontinence and cystitis, was seen in up to 24.5% of patients at all grades following brachytherapy[15]. At grades 2-4, prevalence rates were significantly lower at up to 5.0%. Most grade 3 and 4 urinary morbidity was urinary frequency, incontinence, and ureteral strictures, with grade 3-4 fistula, bleeding, spasm, and cystitis much lower at <1.0% and actuarial 3-year incidence of all grade 3 and 4 urinary morbidity events was 5.3%[15].

In a study of 960 patients, rectal bleeding was seen in 20.1% of patients at grade 1, 6% at grade 2, 1.6% at grade 3, and 0.1% at grade 4[16]. This effect was dose dependent, with patients receiving ≤ 65 Gy having only minor and less frequent adverse events (risk of fistula was 0-2.7%), while patients receiving ≥ 75 Gy had more major and frequent events (12.5% risk of fistula). Overall rectal morbidity ≥ grade 2 was 10% at 69.5 Gy.

In a study of 1176 patients receiving brachytherapy for cervical cancer, grade 3-4 bowel morbidity frequency was 5% at grade 3 and 5.9% at grade 4[17]. Stenosis/stricture/fistula frequency was 2% at grade 3 and 2.6% at grade 4. Less severe events (grade 1 and 2) were more common, with 28-33% experiencing short term diarrhea, flatulence, incontinence, difficulty in controlling bowels, constipation, and abdominal cramps.

Vaginal morbidity with brachytherapy for cervical cancer occurred relatively frequently in the EMBRACE study. In a group of 630 patients, frequency of vaginal stenosis overall was

21%, but the effect was dose-dependent with 20%, 27%, and 34% of patients experiencing grade ≥ 2 events following 65 Gy, 75 Gy, and 85 Gy, respectively[18].

Additionally, patients may experience localized pain during the procedure due to the packing material. It is hypothesized that this will be short term (will resolve within 1 day) and will be significantly decreased during/following treatments with BrachyGel packing.

2.3.2 Known Potential Benefits

Participants may experience less pain and/or side effects of vaginal packing during and following fractions delivered with the BrachyGel Vaginal Hydrogel Packing System than fractions delivered with standard of care packing systems. There should be no difference in experience between arms, as both Arms A and B will undergo two fractions with the Brachygel system and two fractions with the standard of care system.

2.3.3 Assessment of Potential Risks and Benefits

It is expected that brachytherapy fractions delivered with BrachyGel as the packing system will be at least as comfortable and as safe as standard of care. Similarly, the quality of image guidance during fractions delivered with BrachyGel as the packing system should be at least as good as with standard of care packing systems. If BrachyGel is determined to be non-inferior to standard of care options, BrachyGel may present a less expensive, more comfortable, and highly effective option for delivery of brachytherapy for cervical cancer. The risks of participation for individual participants should not be greater than with standard brachytherapy and this study may identify an additional effective, low-cost, comfortable packing system option for future cervical cancer patients requiring brachytherapy.

3 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
To determine if BrachyGel Vaginal Hydrogel Packing System (BrachyGel) is non-inferior to standard method vaginal packing (standard) in dose thresholds for the rectum and the bladder.	The dose to the hottest 2 cc (D2cc) (in Gy) for the rectum and the bladder in periods 1 and 2 (e.g. fractions 2 and 3).
Secondary	
To estimate the difference in the safety profile of BrachyGel compared to standard vaginal packing.	Frequency, intensity, and duration of adverse events in periods 1 to 4 (e.g. fractions 2 through 5).
To estimate period effects in dosimetry thresholds (D0.1cc, D1cc, D2cc) between BrachyGel and standard vaginal packing for the rectum and the bladder.	The dose to the hottest 0.1 cc (D0.1cc), 1 cc (D1cc), and 2 cc (D2cc) (in Gy) for the rectum and the bladder in periods 1 through 4 (e.g. fractions 2 through 5).
Exploratory	
To estimate the difference in participant-reported discomfort between BrachyGel and standard vaginal packing.	Participant-reported discomfort from packing scored on a 4-point scale for periods 1 through 4 (e.g. fractions 2 through 5).

To estimate the difference in physician/physicist evaluation of imaging properties and completeness of packing between BrachyGel and standard vaginal packing.	Physician/physicist evaluation of imaging properties and completeness of packing scored on a 4-point scale for periods 1 through 4 (e.g. fractions 2 through 5).
To estimate the difference in physician-scored use experience between BrachyGel and standard vaginal packing.	Physician-scored use experience scored on a 4-point scale for periods 1 through 4 (e.g. fractions 2 through 5).

4 STUDY DESIGN

4.1 Overall Design

This is a two-center, stratified and randomized, four period, two arm crossover, non-inferiority trial to demonstrate that BrachyGel Vaginal Hydrogel Packing System is non-inferior to standard method vaginal packing (standard).

Two sites are included in the trial design in order to reflect the most common applicators used in intracavitary cervical cancer brachytherapy:

- Tandem and ovoid brachytherapy+/- interstitial needles (UVA cohort)
- Tandem and ring-based brachytherapy +/- interstitial needles (AHN cohort)

The BrachyGel Hydrogel Vaginal Packing System will be compared to gauze packing and/or rectal retractor packing per the institution's standard of care packing practice.

Participants will be stratified by site (UVA/AHN) and randomized to either Arm A or Arm B. Fraction 1 for all participants (both Arms) will be according to standard of care packing and fractions 2-5 (periods 1-4) will alternate between standard of care and BrachyGel packing, as shown in *Figure 1.*

4.2 End of Study Definition

Primary completion date is the date that the final participant was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

Study completion date is the date the final participant was examined or received an intervention for purposes of final collection of data for the primary and secondary outcome measures and adverse events (for example, last participant's last visit), whether the clinical study concluded according to the pre-specified protocol or was terminated.

5 STUDY POPULATION

5.1 Inclusion Criteria

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Biopsy showing cancer of the cervix (squamous cell carcinoma, adenocarcinoma, adenosquamous, neuroendocrine, etc)

2. FIGO IB1 – IVB Staging according to FIGO and TNM guidelines
3. Planning to receive brachytherapy as a part of the definitive treatment for cervical cancer
4. Karnofsky performance status (KPS) ≥ 70 or ECOG status ≤1
5. Stated willingness to comply with all study procedures and availability for the duration of the study
6. Age ≥ 18 years
7. Agreement to adhere to Lifestyle Considerations (see *section 5.3*) throughout study duration

5.2 Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. History of pelvis or abdominal radiation therapy (RT) that is not a part of the definitive treatment plan for the cancer of interest"
2. History of total or partial hysterectomy
3. Plan to receive external beam RT (EBRT) alone as the definitive treatment plan for the cancer of interest
4. Known pregnancy or lactation (no pregnancy test required prior to participation)
5. Known contraindications to brachytherapy

5.3 Lifestyle Considerations

During this study, women of childbearing potential are required to use highly effective contraception methods following study entry and through the last fraction of brachytherapy.

Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone level > 35 mIU/mL).

The following birth control methods are allowed during the study:

1. Barrier methods
   a. Diaphragm with spermicide
   b. Cervical cap with spermicide
   c. Condom with spermicide
2. Hormonal methods
   a. Hormonal contraceptives (such as the birth control pill)
   b. Intra-uterine device (IUD)
3. Abstinence (no heterosexual activity)

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent

reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (for NIH studies) and to respond to queries from regulatory authorities. Minimal information includes demography and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial because of a modifiable factor may be rescreened.

6 STUDY INTERVENTION

6.1 Description of Study Intervention(s)

Participants will be assigned to Arm A or Arm B, as described in section 4.1 and Figure 1. Fraction 1 for all participants (both Arms) will receiving standard of care packing. During fractions 2-5 of brachytherapy, participants will have vaginal packing alternating between the BrachyGel Vaginal Hydrogel Packing System and standard of care vaginal packing, strategy which will include gauze vaginal packing or rectal retractor.

For Arm A of the study, the BrachyGel Packing System will be used during fractions 3 and 5. Standard packing will be used for fractions 1, 2 and 4.

For Arm B of the study, the BrachyGel Packing System will be used during fractions 2 and 4. Standard packing will be used for fractions 1, 3 and 5.

6.2 Dosing and Administration

6.2.1 Dose Delays

Delays in brachytherapy fractions will be according to institutional guidelines.

6.3 Preparation/Handling/Storage/Accountability

6.3.1 Acquisition and Accountability

The investigational devices will be stored in a secure area. Each package of the Brachygel Vaginal Hydrogel Packing System will be single-use specific to a particular participant and any remaining packs will be destroyed in accordance with institutional policies, as directed by Brachyfoam.

6.3.2 Appearance, Packaging, and Labeling

Details on the appearance, packaging and labeling may be found in the clinical use instructions provided. The device will be labeled in accordance with 21 CFR 812.5 and will include the following information: lot number, quantity of contents, name and place of business of the manufacturer, packer or distributor, and the required investigational device statement (“CAUTION: --Investigational device. Limited by Federal (or United States) law to investigational use”). The labeling will also include relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings or precautions.

6.3.3 Product Storage and Stability

The device will be stored by the study team at a temperature between 35 and 72 degrees Fahrenheit (2 and 22 degrees Celsius). The product is stable with these conditions for at least 6 months after manufacture.

6.3.4 Preparation

Please see the clinical use instructions provided for this information.

6.4 Registration and Randomization

All participants must sign the consent form prior to determination of eligibility for this study.

When a site is ready to enroll a patient, the following documentation must be scanned and emailed to the UVA Coordinating Center:

- Patient and staff signed signature page of the current informed consent form (ICF)
- Completed Inclusion/Exclusion checklist demonstrating subject eligibility
- Supporting documentation needed to confirm eligibility (lab results, scan results etc.)

Consult the Study Reference Manual for instructions on sending this information. The Coordinating Center will consult with the Overall Study PI if questions arise in confirming eligibility. The UVA Coordinating Center will communicate the subject number and arm assignment to the enrolling site.

Registration will occur following verification of eligibility by the treating physician. Eligibility confirmation and registration can occur after the 1st brachytherapy fraction but must occur before the 2nd brachytherapy fraction.

Participants who are consented and accrued to the study should be registered in the designated EDC System in accordance with the Clinical Trial Management System Policy. General guidelines are available in the User Manual and Data Entry Guide.

Participants should receive their first fraction of brachytherapy within 14 days of registration.

Randomization will be discussed with participants during the process of informed consent, and informed consent must be documented prior to randomization. Randomization will be stratified by institution, and will be based on equal allocation between arms. The randomization sequences will be generated by the study statisticians and loaded into RAND and accessed in the designated EDC System. Randomization will occur no sooner than 10 days prior to the second fraction of brachytherapy.

This study does not involve any blinding or masking procedures. Participants will be told which arm they are assigned to.

6.5 Concomitant Therapy

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in

the Case Report Form (CRF) are medications used for pain control for each brachytherapy procedure.

6.5.1 Rescue Medicine/Supportive Care

Supportive care should be according to institutional guidelines.

7 STUDY CLOSURE, STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION OR WITHDRAWAL

7.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, funding agency, and regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform the Institutional Review Board (IRB) and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that would warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Change in funding status

If the study is halted due to safety concerns, protocol compliance and/or data quality, the study may resume once these concerns are addressed and satisfy the IRB and Data and Safety Monitoring Committee.

Participants receiving the study intervention at the time of study discontinuation should complete procedures described in *section 7.3*.

7.2 Participant Discontinuation/Withdrawal

Participants are free to withdraw from participation in the study at any time upon request.

A participant's study treatment would be discontinued for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- Severe, CTCAE Grade ≥ 4 adverse event considered at least possibly related to the packing procedure
- Participant is unable to receive further brachytherapy due to an adverse event or a change in status (e.g. decline due to disease, change in goals of care, development of metastases).
- Participant decision to withdraw from study treatment and/or the study

The reason for participant discontinuation or withdrawal from study treatment will be recorded on the case report form. Participants that withdraw from study treatment only, will continue with study follow-up. Participants that withdraw from study treatment and study follow-up will not be contacted for any further study visits.

7.3 Procedures for Discontinuation of Study Intervention

Discontinuation from brachytherapy according to the study does not mean discontinuation from the study, and remaining study procedures should be completed as indicated by the study protocol. If a clinically significant finding is identified (including, but not limited to changes from baseline) after enrollment, the investigator or qualified designee will determine if any change in participant management is needed. Any new clinically relevant finding will be reported as an adverse event (AE).

The data to be collected and procedures to be completed at the time of study intervention discontinuation are included in the schedule of assessments in *section 13.1*.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 Clinical Assessments

8.1.1 Physical Exam

A complete physical exam will be completed at screening. Karnofsky performance status (KPS) or ECOG status will be collected at the time of each physical exam.

8.1.2 Assessment of Adverse Events

Each participant will be evaluated by a licensed clinician at each study visit. The NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be used for the characterization and grading of adverse events.

8.2 Participant Reported Outcomes

Participant-reported discomfort during both standard and BrachyGel packing placement/removal will be assessed following fractions 2-5 of brachytherapy. See *section 13.3* for the questions included. The participant will either be given a paper survey of the questions to complete or a member of the clinical or study team will read the questions and possible responses to the participant and the responses will be recorded at that time. The questions must be answered directly following the completion of brachytherapy within 1 hour of removal of packing.

If the participant is sedated for a particular brachytherapy fraction, the participant will not complete the participant discomfort survey questions for that fraction.

8.3 Physicist and Physician Assessments

Physician & physicists will evaluate imaging properties, completeness of packing and general experience of using each packing systems (both standard of care and Brachygel)

following fractions 2-5 for each participant. Only the dosimetry measurements will be collected for the first fraction. See *sections 13.2* and *13.4* for the instruments.

9 DATA AND SAFETY MONITORING PLAN

9.1 Adverse Events and Serious Adverse Events

9.1.1 Definition of Adverse Events (AE)

For the purposes of this protocol, we define an adverse event to be any untoward medical occurrence associated (at least possibly related) with the use of the study intervention(s)

9.1.2 Definition of Serious Adverse Events (SAE)

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening adverse event,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A planned medical or surgical procedure is not, in itself, an SAE.

9.1.3 Classification of an Adverse Event

9.1.3.1 Severity of Event

For adverse events (AEs) not included in CTCAE version 5.0, the following guidelines will be used to describe severity.

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.

- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

9.1.3.2 Relationship to Study Intervention

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. Relationship of the adverse event to brachytherapy and packing system will be assessed separately. In a clinical trial, the study product must always be suspect.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to study intervention administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the study intervention (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.

- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time after administration of the study intervention, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.

- **Unlikely to be related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to study intervention administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the study intervention) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).

- **Not Related** – The AE is completely independent of study intervention administration, and/or evidence exists that the event is definitely related to another

etiology. There must be an alternative, definitive etiology documented by the clinician.

9.1.3.3 Expectedness

The treating investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention and/or this population. Expected AEs are described in *Table 2.*

Table 2

Adverse event	Maximum grade expected
Diarrhea	3
Cystitis	2
Rectal perforation	3
Rectal fistula	3
Proctitis	3
Rectal pain	2
Rectal hemorrhage	3
Bowel perforation	3
Bladder perforation	2
Hematuria	2
Urinary frequency	2
Urinary incontinence	2
Urinary urgency	2
Pelvic pain	2
Vaginal perforation	3
Vaginal hemorrhage	2

9.1.4 Abnormal Laboratory Values

Laboratory values will not be collected or assessed for this study. Abnormal laboratory values will not be recorded or reported in this study.

9.1.5 Time Period and Frequency for Event Assessment and Follow-Up

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

Study staff will record all reportable events with start dates occurring any time after brachytherapy fraction 2 is completed until 30 days (for non-serious AEs) or anytime (for SAEs considered related to the study intervention) after the last day of study treatment. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

9.1.6 Adverse Event Reporting

AEs must be recorded into the EDC system designated by the University of Virginia database, per the following guidelines.

Table 3

Table 3: High Risk Studies
Reporting requirements for AEs that occur within 30 days of the last dose of protocol specified treatment

	Grade 1	Grade 2		Grade 3				Grade 4 & 5
				Expected		Unexpected		
	Expected and Unexpected	Expected	Unexpected	Without hospitalization	With hospitalization	Without hospitalization	With hospitalization	Expected and Unexpected
Unrelated Unlikely	30 days	30 days	30 days	30 days	15 days	30 days	15 days	7 days
Possible Probable Definite	30 days	30 days	15 days	30 days	15 days	7 days	7 days	(24-hrs)* 7 days

*Enter into Cancer Center database within 24 hours if unexpected and definitely related to protocol specified treatment
Hospitalization defined as an inpatient hospital stay or prolongation of a hospital stay equal to or greater than 24 hours

9.1.7 Serious Adverse Event Reporting

The study clinician will report to the overall study PI any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or clinical use instructions, and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. See Study Reference Manual for contact information and instructions for reporting.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the UVA Coordinating Center (UVA CC) and should be provided as soon as possible.

Site Reporting Requirements

<u>Any Event Resulting in death that is deemed DEFINITELY related to (caused by) study participation</u>

OR

Any event deemed serious

- Report to the UVA CC within 24 hours from the time the study team received knowledge of the event according to UVA CC requirements.
- Non relying sites: report to your IRB in accordance with your IRB guidelines.
- Relying sites (use the UVA IRB-HSR as the IRB of record): the UVA CC will report to the UVA IRB-HSR in accordance with the guidelines.
- UVA site: report to the UVA IRB-HSR in accordance with the guidelines.

UVA Reporting Guidelines

- Notify the UVA IRB-HSR of any event resulting in death that is deemed DEFINITELY related to (caused by) study within 24 hours from the time the study team received knowledge of the event. Report using IRB Online and by telephone.
- Notify the UVA IRB-HSR of any serious, unexpected and related adverse event within 7 calendar days from the time the study team receives knowledge of the event. Timeline includes submission of signed hardcopy of AE form. Report using IRB online.
- For events considered at least possibly related to BrachyGel, notify Brachyfoam within 72 hours of UVA CC's awareness of the event. To do so, email *tshowalter.brachyfoam@gmail.com*.

9.2 Unanticipated Adverse Device Effects

9.2.1 Definition of Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect is any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

9.2.2 Reporting of UADE

Site Reporting Requirements

- The study investigator shall complete an Unanticipated Adverse Device Effect Form and submit to the UVA CC and to the reviewing Institutional Review Board (IRB) according to the IRB's guidelines, but in no event later than 10 working days after the investigator first learns of the effect.

- Non relying sites: report to your IRB in accordance with your IRB guidelines.
- Relying sites (use the UVA IRB-HSR as the IRB of record): report to the UVA CC within 5 calendar days so that the UVA CC can report to the reviewing IRB within 10 calendar days.
- UVA site: report to the UVA CC within 5 calendar days so that the UVA CC can report to the reviewing IRB within 10 calendar days.

UVA Reporting Guidelines

- The UVA CC is responsible for conducting an evaluation of an unanticipated adverse device effect and shall report the results of such evaluation to all reviewing IRBs and participating investigators within 10 working days after the UVA CC first receives notice of the effect. Thereafter, the UVA CC shall submit such additional reports concerning the effect as the IRBs/participating investigator requests.
- If the PI or UVA DSMC determine that an unanticipated adverse device effect presents an unreasonable risk to subjects shall terminate all investigations or parts of investigations presenting the risk as soon as possible. Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the UVA CC first received notice of the effect.
- For events considered at least possibly related to BrachyGel, notify Brachyfoam within 72 hours of UVA CC's awareness of the event. To do so, email *tshowalter.brachyfoam@gmail.com*.

9.3 Reporting Events to Participants

If there is any new information relevant to the participant's willingness to continue to participate in the study, such as if there are new risks of the study treatment identified that were not included on the consent form that the participant signed, the study team will contact the participant to discuss this information. If the participant is still receiving study treatment, the study team will present the participant with an updated consent and confirm that he or she wants to continue receiving study treatment. Each site PI will determine whether new risks are applicable to participants who are in follow-up, whether participants need to be notified, and whether re-consenting is required.

9.4 Reporting of Pregnancy

Pregnancy does not need to be reported to UVA IRB-HSR. Women found to be pregnant should not receive any further brachytherapy. While the study intervention (packing system type) should not affect pregnant women or the unborn child, pregnant women should not receive radiation in this area.

9.5 Unanticipated Problems

9.5.1 Definition of Unanticipated Problems (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems (UPs)(may include a data breach) involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.
- This definition could include an unanticipated adverse device effect. Please refer to *section 9.2.1* for the definition of an unanticipated adverse device effect.

9.5.2 Unanticipated Problem Reporting

Site Reporting Requirements

- UPs that are SAEs will be reported in accordance with the guidelines for SAE reporting.

- UPs that are not adverse events, protocol deviations or data breaches (see *section 9.6* for reporting for data breaches)
  - Report to the UVA CC within 2 calendar days from the time the study team receives knowledge of the event.
  - Non- relying sites: Report to your IRB of record in accordance with your IRB guidelines.
  - Relying sites (use the UVA IRB-HSR as the IRB of record): the UVA CC will report to the UVA IRB-HSR in accordance with the guidelines.
  - UVA Site: report to the UVA IRB-HSR in accordance with the guidelines—see sponsor reporting requirements.

UVA Reporting Guidelines

- Report UPs that are not adverse events or protocol deviations to the UVA IRB-HSR within 7 calendar days from the time the study team receives knowledge of the event. Report using the Unanticipated Problem Report form.
- Report to Brachyfoam within 48 hours of UVA CC's awareness of the event. To do so, email *tshowalter.brachyfoam@gmail.com*.
- All UPs will be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and the Office for Human Research Protections (OHRP) in accordance with institutional policies.

An unanticipated device effect may also qualify as an unanticipated problem. Please follow the guidelines for reporting UADEs in *section 9.2.2*.

9.5.3 Reporting Unanticipated Problems to Participants

If during the course of the study there is an unanticipated problem that affects current or past participants, affected participants will be contacted if needed.

9.6 Data Breach

9.6.1 Definition of Data Breach

An unauthorized acquisition, access, or use of protected health information (PHI) that compromises the security or privacy of such information.

9.6.2 Reporting a Data Breach

Site Reporting Requirements

- Report to the UVA CC within 24 hours from the time the study team receives knowledge of the event.
- Non- relying sites: Report to your IRB of record in accordance with your IRB guidelines.
- Relying sites (use the UVA IRB-HSR as the IRB of record): the UVA CC will report to the UVA IRB-HSR in accordance with the guidelines.
- UVA Site: report to the UVA IRB-HSR in accordance with the guidelines.

UVA Reporting Guidelines

- Report to the UVA Corporate Compliance and Privacy Office as soon as possible and no later than 24 hours from the time the incident is identified. Report by telephone.
- Report to ITC if the breach involves electronic data. Report as soon as possible and no later than 24 hours from the time the incident is identified. Refer to the following for details: *http://security.virginia.edu/report-information-security-incident*.
- Report to UVA police if the breach includes such things as stolen computers. Report by telephone.
- Report to Brachyfoam within 48 hours of UVA CC's awareness of the event. To do so, email *tshowalter.brachyfoam@gmail.com*.

9.7 Protocol Deviation

9.7.1 Definition of Protocol Deviation

A protocol deviation is defined as any change, deviation, or departure from the study design or procedures of a research project that is NOT approved by the institution's IRB prior to its initiation or implementation, OR deviation from standard operating procedures, Good Clinical Practices (GCPs), federal, state or local regulations. Protocol violations may or may not be under the control of the study team or UVA staff. These protocol violations may be major or minor violations.

9.7.2 Protocol Exception

Protocol exceptions are circumstances in which the investigator wishes to deviate from eligibility criteria or one or more of the specific procedures called for in a research plan. Unlike modifications that apply to all subsequent subjects in the research, a protocol/research plan exception only applies to a specific subject or group of subjects. Exceptions are planned, and the investigator gets approval from the lead site ahead of time. Such a request should be rare and justified in terms of serving the best interests of the potential study participant. The Lead site will receive permission from the DSMB for any exceptions at the Lead site.

9.7.3 Reporting of a Protocol Deviation or Exception

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents.

Site Reporting Requirements: Major Deviations Only

- Report to the UVA CC within 4 calendar days from the time the study team receives knowledge of the event.
- Non- relying sites: Report to your IRB of record in accordance with your IRB guidelines.
- Relying sites (use the UVA IRB-HSR as the IRB of record): the UVA CC will report to the UVA IRB-HSR in accordance with the guidelines—see sponsor reporting requirements.
- UVA Site: report to the UVA IRB-HSR in accordance with the guidelines—see sponsor reporting requirements.

UVA Reporting Guidelines

- Report to the UVA IRB-HSR major deviations within 7 calendar days from the time the study team received knowledge of the event. Report using the Protocol Deviation and Protocol Exception Reporting Form.
- Report major deviations to Brachyfoam within 7 calendar days of UVA CC's awareness of the event.
- Minor deviations do not need to be reported to the UVA IRB-HSR. Refer to the Study Reference Manual for instructions on recording minor deviations.

9.8 Participant Withdrawals/Dropouts Prior to Study Completion

Participants who withdraw consent and those dropping out of the study secondary to an AE will be reported to the UVA IRB yearly on the IRB continuation form.

10 STATISTICAL CONSIDERATIONS

10.1 Design

This is a two-center, stratified and randomized, four period, two arm crossover, non-inferiority trial to demonstrate that BrachyGel Vaginal Hydrogel Packing System (hydrogel) is non- inferior to standard method vaginal packing (standard) in dose thresholds for D2cc (in Gy) for rectum and bladder by more than a non-inferiority margin of δ=1 Gy. Outcomes will be measured after each of 5 treatment fractions with results from the 1st fraction serving as the baseline measurement for each participant. D2cc measurements within organs varies between fractions as well as by participants, thus, each participant will receive both types of vaginal packing with order of packing type being chosen at random. Specifically, all participants will receive the standard method during the 1st fraction and then either sequence A (standard-hydrogel-standard-hydrogel) or sequence B (hydrogel-standard-hydrogel-standard) chosen at random, for the remaining four fractions. It is possible for participants to require less therapy during the final fraction (ie maximum therapy has been applied to the tumor), thus, the choice of ordering is limited to these two orderings to ensure that both packing types are administered to each participant with the primary assessment based upon fraction 2 and 3 data (ie, a two period, two treatment crossover).

10.2 Randomization and Stratification

Participants will be stratified by site (UVA, AHN). Randomization will occur with equal allocation to each ordering (Arm A or Arm B) using a stratified block randomization scheme with varying block sizes (of 2-4). Randomization will occur prior to the 2nd fraction of brachytherapy.

10.3 Evaluation of Sample Populations and Criteria

10.3.1 Study Population

Safety: All randomized participants receiving at any protocol treatment will be evaluated for safety outcomes.

Evaluable: All randomized eligible participants receiving at least 3 fractions of treatment will be evaluated for study outcomes.

10.3.2 Study Outcomes & Endpoints

Study measurements will be captured post each fraction of treatment. Assessments may include:

- Adverse events
- Dosimetry
- Physicist evaluation of imaging/packing
- Physician evaluation of imaging/packing
- Participant discomfort survey

There are two primary endpoints based upon dosimetry measurements in the bladder and the rectum. Each endpoint is the difference between D2cc dosimetry measurements obtained during periods 1 and 2 (fractions 2 and 3 under the 2x2 crossover structure). Additional assessments include data from periods 3 and 4 (fractions 4 and 5).

Additional endpoints include measurements over all periods for:

- Bladder and rectal dosimetry as measured by D0.1 cc and D1 cc.
- Participant reported discomfort
- Physicist evaluated imaging properties
- Physician evaluated imaging properties
- Physician evaluated use experience

10.4 Sample Size and Accrual

For this crossover study the primary comparison is based upon the 2x2 initial crossover portion. The primary endpoint is the difference of D2cc dosimetry measurements between periods 1 and 2 (fractions 2 and 3) for sequence arm A and sequence arm B based upon a two-sample comparison of the mean difference to the non-inferiority margin. Data from 51 patients treated at UVA with fraction 2 and 3 information, reported overall in Romano et al 2018[19], with standard packing resulted in a mean (standard deviation) of 0.12 (1.56) and 0.10 (0.92) D2cc for the difference for bladder and rectal dosimetry, respectively. The

width of the 95% CI for the mean difference was 0.9 and 0.5 for bladder and rectal dosimetry, respectively. Based upon these measurements and clinical judgement, a non-inferiority margin of δ=(0.12+1.56=1.68) was chosen for this study.

Justification for the sample size is based upon obtaining sufficient accrual to test the primary hypothesis that use of the hydrogel vaginal packing is non-inferior to standard packing methods in 1) bladder and 2) rectal dosimetry by more than a non-inferiority margin. Let $diff_A$ and $diff_B$ denote the differences between fractions.

The primary hypothesis to be tested is H_o: $\mu_{diffA} - \mu_{diffB} \geq \delta$ versus H_a: $\mu_{diffA} - \mu_{diffB} < \delta$, where the non-inferiority margin, δ=1.68, *each* for bladder and rectal, with a one-sided 2.5% level t-test. A sample size of 20 evaluable cervical cancer participants per arm achieves 94% power to detect non-inferiority using a one-sided t-test when the margin of non-inferiority is 1.68, the true difference between the means and the reference (standard) value is 0.12, and the assume population standard deviation is 1.56. Power is 96% if one uses the estimates for rectal dosimetry.

Adjusting for participants not satisfying the evaluable criteria (*section 10.3.1*), it is estimated that approximately 57 cervical cancer participants will need to be accrued to the study in order to test the primary study hypothesis. Each site may allow up to 10 oncologist and 4 physicists/dosimetrist to participate in completing the Physician and Physicist Assessments.

10.5 Safety Monitoring

All study participants who receive treatment will be assessed for the occurrence of treatment related adverse events. Adverse events of potential concern related to the vaginal packing, are acute vaginal adverse events (aVAE) which: i) is determined to be at least possibly related to BrachyGel; ii) occurs within the first 30 days from 1st Brachytherapy treatment utilizing BrachyGel (ie. Period 2 or 3 depending on the randomization arm); and iii) meets the criterion below:

Has any of the following vaginal toxicities grade >=3 according to CTCAE:

- Vaginal pain
- Vaginal perforation
- Vaginal hemorrhage
- Vaginal inflammation
- Vaginal infection
- Dyspareunia

Safety will be assessed by monitoring the number of participants who experience an aVAE. Results reported in Romano et al 2017 on high-dose brachytherapy experience at UVA noted that 0/74 = 0% (upper limit of 95% CI of 4.9%) patients experienced grade ≥3 aVAE.[20] Others have reported similarly low rates with at most 2% for late vaginal toxicity.[21,22] For this study the upper boundary of a sequential probability ratio test (SPRT) based upon a binomial test of proportions for aVAE will be used for monitoring, to protect against excessive aVAE rates. The stopping boundary is for a SPRT contrasting a null 4% versus an unacceptable 9% aVAE rate, with nominal type I and II errors of 10% and 10%, respectively. The slope of the parallel line for monitoring is 2.54 and the intercept is 0.062.

Safety stopping guidelines for the occurrence of aVAEs are detailed in the following table. If a stopping bound is crossed then accrual to the study will be suspended until the study PI, co-investigators and the DSMC can review the data, and determine if the study should continue, be amended or be closed to further accrual.

Number of participants who received BrachyGel	Number with grade ≥ 3 aVAE
3-7	≥ 3
8-23	≥ 4
24-39	≥ 5
40-45	≥ 6

10.6 Analyses

Two main sets of analyses for all endpoints are proposed. The first limits assessment to data from periods 1 and 2, and the second uses data from all periods. The first set will summarize data based upon differences between period endpoints, with comparisons by arm. The second will employ repeated measure models to estimate period effects.

For fractions 2-5, adverse events will be summarized by frequency and severity and packing type. For the ordinal measures, mean differences and 95% confidence intervals for the difference will be calculated by packing type. Repeated measure models will be used to describe treatment' effects over time and F-tests will be used to assess period affects. Graphical methods will aid in assessing model assumptions.

11 REGULATORY AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory and Ethical Considerations

11.1.1 Informed Consent Document

Consent forms will be written in accord with federal regulations and will be reviewed and approved by the UVA IRB-HSR prior to use. Signed consent forms and other research records will be retained in a confidential manner.

11.1.2 Consent Procedures and Documentation

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. A member of the study team will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to

discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Results from procedures completed prior to consent for standard of care purposes may be used for research purposes. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

Doctors and physicists who plan to complete the Physician and Physicist Assessment Surveys are considered participants. A member of the study team will explain the research study and allow the individual to review the protocol. Doctor and physicist participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. Doctors and physicists will give verbal consent to participate.

11.1.3 Confidentiality and Privacy

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. Consents will be maintained in a confidential manner in accordance with the code of federal regulations and HIPAA. When possible, specimens will be coded with IDs (not MRN or name). No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be entered and stored in the designated EDC System. This will include limited participant identifying information, including participants' initials and dates of birth. Individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and UVA CC research staff will be secured and password protected.

Certificate of Confidentiality

To further protect the privacy of study participants, a site may apply for a Certificate of Confidentiality. For NIH studies, this will automatically be issued by the National Institutes of Health (NIH) and an application is not necessary. This certificate protects identifiable research information from forced disclosure. It allows the investigator and others who have access to research records to refuse to disclose identifying information on research participation in any civil, criminal, administrative, legislative, or other proceeding, whether at the federal, state, or local level. By protecting researchers and institutions from being compelled to disclose information that would identify research participants, Certificates of Confidentiality help achieve the research objectives and promote participation in studies by helping assure confidentiality and privacy to participants.

11.1.4 Safety Oversight

The University of Virginia Cancer Center Data and Safety Monitoring Committee (CC DSMC) will provide oversight of the conduct of this study. The CC DSMC will report to the UVA Protocol Review Committee (PRC).

The UVA CC DSMC will review the following:

- All adverse events
- Audit results
- Application of study designed stopping/decision rules
- Whether the study accrual pattern warrants continuation/action
- Protocol violations

The UVA CC DSMC will meet every month for aggregate review of data. Tracking reports of the meetings are available to the PI for review. Issues of immediate concern by the DSMC are brought to the attention of the sponsor (and if appropriate to the PRC and IRB) and a formal response from the sponsor is requested. Per the UVA Cancer Center NIH approved institutional plan, this study will be audited approximately every 6 months. The audit may include direct access to source data/documents.

Any study under the purview of the University of Virginia IRB-HSR is subject to review of files at the University of Virginia. Studies are chosen for Post-approval Monitoring either a) at random or b) requested by a study team member or any member of the IRB-HSR.

The purpose of Post-approval Monitoring audits is to ensure that documentation of clinical research studies is of the highest quality, verify protocol adherence, and ensure that all Federal and local rules concerning clinical research are being fulfilled. Post-approval monitoring is done by staff within the office of the Vice President for Research (VPR) in accordance with their Standard Operating Procedures. The conduct of an on-site review may include but is not limited to:

- requests for progress reports from investigators,
- examinations of research records, including signed informed consent documents, protocol modifications, and unexpected, serious, and/or related adverse experience reports,
- contacts with research subjects, or
- observation of the consent process and/or research procedures. Examples of when observation of the consent process could occur are:

- Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
- IRB is made aware of a complaint or concern with regard to the informed consent process; or
- IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

Limited monitoring will be conducted by a quality assurance team at the Allegheny Health Network. This includes the following patient related data such as eligibility review and data source verification. SAEs will also be reviewed by a safety team at the Allegheny Health Network.
The quality assurance team does not review:

- contacts with research subjects, or
- observation of the consent process and/or research procedures. Examples of when observation of the consent process could occur are:
  - Full board IRB determines during review of a project that a conflict of interest exists such that the informed consent process should be observed by a neutral party;
  - IRB is made aware of a complaint or concern with regard to the informed consent process; or
  - IRB determines as a result of the monitoring process that the consent process is insufficient and education/training is required for conduct of consent.

11.1.5 Site Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

- The UVA Coordinating Center will implement ongoing monitoring activities for this study to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and subject safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion.

- Monitoring may be conducted either remotely or on-site. For remote visits, each institution will be required to provide redacted source documents for review or appropriate access to the EMR. The UVA CC will provide the Participating Institution with a follow-up letter following completion of the monitoring visit which should be maintained in the site regulatory files. The schedule for monitoring may be adjusted according to subject accrual and data quality. The Investigator will be notified in advance of each visit.

- Independent audits may be conducted by each institution according to institutional guidelines. Results of these audits may be requested by the UVA Coordinating Center.

11.1.6 Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion according to institutional policies.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

11.2 Data Handling and Record Keeping

11.2.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data will be collected using a password-protected, centralized electronic case report form system. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

11.2.2 Study Records Retention

Study documents should be retained for a minimum of 2 years after the date of the release for commercial distribution by the manufacturer or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when these documents no longer need to be retained. Record retention will be in accord with 21 CFR 62 and HIPAA regulations.

11.3 Publication and Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

11.4 Conflict of Interest Policy

The independence of this study from any actual or perceived influence, such as by industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with the institution has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

Dr. Timothy Showalter, an investigator for this study, is also the chief medical officer and founder of Brachyfoam, the manufacturer of the BrachyGel Vaginal Hydrogel Packing System used in this study. He will serve as a resource for study design and planning, but will not enroll patients, or supervise any students or trainees involved in research on this project as pertains to the data collection and analysis of results. He will administer brachytherapy during about half of the fractions administered at UVA. When he administers brachytherapy, he will not complete the physician questionnaire. In these instances, Dr. Romano will complete the part of the questionnaire related to completeness and imaging clarity of packing and the question related to ease of use will be left blank.

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13 APPENDICES

13.1 Schedule of Activities (SoA)

Procedures	Screening (within 6 weeks of Brachytherapy 1)	Brachytherapy 1	Brachytherapy 2	Brachytherapy 3	Brachytherapy 4	Brachytherapy 5	30 Day +/- 2 weeks Safety Follow-up
Informed consent	X						
Demographics	X						
Baseline conditions/assessment	X[2]						
Randomization			X[5]				
Brachytherapy[1]		X[4]	X	X	X	X	
Physical exam	X[2]						X
Performance status	X[2]						X
Concomitant medications related to pain control during procedure[7]			X	X	X	X	
Physician Assessments of imaging/packing experience			X	X	X	X	
Physicist Assessments of imaging/packing experience		X[6]	X	X	X	X	
Participant survey[3]			X	X	X	X	
Adverse event review and evaluation			X----------X				X

[1] Alternations will be based on Arm Assignment according to *Figure 1*.

[2] Must occur within 30 days of Brachytherapy 1. The assessments can be collected on the same day as Brachytherapy 1.

[3] Participant survey should be completed without 1 hour following removal of packing after completion of brachytherapy. Not collected if participant was sedated.

[4] Brachytherapy 1 is considered to be a part of the screening visit. Brachytherapy 2 is considered to be the "start of treatment." Brachytherapy 1 must occur within 14 days of registration.

[5] No sooner than 10 days before Brachytherapy 2.

[6] Only the dosimetry measurements need to be collected for Brachytherapy 1.

[7] Not collected if participant was sedated.

13.2 Physicist/Dosimetrist Case Report Form

Date: _____

Subject ID: _____

Fraction: _____ of 5

Packing Method: _____

Applicator: _____

Prescription dose: _____ Gy

HR-CTV D90: _____ Gy

Bladder:
D0.1 cc: _____ Gy

D1 cc: _____ Gy

D2cc: _____ Gy

Rectum:
D0.1 cc: _____ Gy

D1 cc: _____ Gy

D2cc: _____ Gy

1. Please rate the completeness of the packing by **clearly selecting** the most appropriate response below:

   ◯ N/A (1st Brachytherapy Fraction)
   ◯ Excellent filling of space
   ◯ Good filling of space
   ◯ Fair filling of space
   ◯ Poor filling of space

2. Please rate the imaging clarity of the packing (i.e. ability to discern packing from pelvic organs) by **clearly selecting** the most appropriate response below:

   ◯ N/A (1st Brachytherapy Fraction)
   ◯ Very clear distinction between packing and OARs (organs at risk)
   ◯ Clear distinction between packing and OARs (organs at risk)
   ◯ Poor distinction between packing and OARs (organs at risk)
   ◯ No distinction between packing and OARs (organs at risk)

_____ _____ _____
Print Name Signature Date

13.3 Participant Packing Discomfort Assessment / Evaluación de la Incomodidad del Empaque de la Participante

Date/Fecha: _____

Subject ID/ ID del Sujeto: _____

Fraction/ Fracción: _____ of 5

Packing Method/ Método de Empaque: _____

Applicator/ Aplicador: _____

1. Please rate your discomfort during the entire brachytherapy treatment. / Califique su malestar durante todo el tratamiento de braquiterapia

- ◯ No discomfort/ Sin molestias
- ◯ Mild discomfort/ Molestias leves
- ◯ Moderate discomfort/ Molestias moderadas
- ◯ Severe discomfort/ Molestias severas

2. Please rate your discomfort during the vaginal packing placement and removal. / Califique su molestia durante la colocación y extracción del empaque vaginal.

- ◯ No discomfort/ Sin molestias
- ◯ Mild discomfort/ Molestias leves
- ◯ Moderate discomfort/ Molestias moderadas
- ◯ Severe discomfort/ Molestias severas

Questionnaire Completed by/ Cuestionario completado por:

◯ Participant/ Participante ◯ Administrator/ Administrador

_____	_____	_____
Print Name/ Escriba su Nombre	Signature/ Firma	Date/Fecha

13.4 Physician Case Report Form

Date: _____

Subject ID: _____

Fraction: _____ of 5

Packing Method: _____

Applicator: _____

1. Please rate the completeness of the packing by **clearly selecting** the most appropriate response below:

   ◯ Excellent filling of space
   ◯ Good filling of space
   ◯ Fair filling of space
   ◯ Poor filling of space

2. Please rate the imaging clarity of the packing (i.e. ability to discern packing from pelvic organs) by **clearly selecting** the most appropriate response below:

   ◯ Very clear distinction between packing and OARs (organs at risk)
   ◯ Clear distinction between packing and OARs (organs at risk)
   ◯ Poor distinction between packing and OARs (organs at risk)
   ◯ No distinction between packing and OARs (organs at risk)

3. Please rate the ease of packing placement and removal by **clearly selecting** the most appropriate response below:

   ◯ Extremely easy
   ◯ Somewhat easy
   ◯ Somewhat difficult
   ◯ Extremely difficult
   ◯ Unable to rate

_____	_____	_____
Print Name	Signature	Date

13.5 Protocol Amendment History

Version Date: from 3/31/2021 to 11/16/2021

Section(s)	Description of Change
Title Page, Key Roles and Study Governance, ABBREVIATIONS, 1.1 Synopsis, 4.1 Overall Study Design, 10.2 Randomization and Stratification, 11.1.4 Safety Oversight	Updated site contact information and changed UPMC to AHN.
Rationale: UPMC has not/will not be participating as an additional site for the trial. The additional site has been changed to AHN.	
8.2 Participant reported outcomes	Reworded to include the options for completing the participant surveys. Participants can either complete a paper survey of the questions or a team member can read the questions/answers and record the participant's selections.
Rationale: For flexibility, there is no impact in having participants answer the questions on paper independently.	
9.1.1 Definition of Adverse Events (AE)	Redefined AEs to be any untoward medical occurrence associated (at least possibly related) with the use of the study intervention(s)
Rationale: The new definition streamlines the capture of AEs without underreporting. This definition captures pertinent standard clinical care and intervention related AEs of any category.	
9.1.7 Serious Adverse Event Reporting, 9.2.2 Reporting of UADE, 9.5.2 Unanticipated Problem Reporting, 9.6.2 Reporting a Data Breach, 9.7.3 Reporting of a Protocol Deviation or Exception	Restructured the reporting guidelines to specify which entities perform which requirements based on site type.
Rationale: For clarity on which requirements are performed by the UVA Coordinating Center and which are performed by the UVA site study team.	
10.4 Sample Size and Accrual	Changed the total maximum enrollment goal from 70 to 57
Rationale: To better align with the study budget.	
13.1 Schedule of Activities (SoA)	Updated calendar footnotes and increased timeframe for the collection of baseline physical exam, performance evaluation and conditions from within 3 days of Brachytherapy 1 to 30days.
Rationale: For clarity and to align with SOC practice.	
13.2 Physicist/Dosimetrist Case Report Form, 13.3 Participant Packing Discomfort Assessment, 13.4 Physician Case Report Form	Updated formatting of Questionnaires and added Spanish translation to the participant discomfort survey.
Rationale: For functionality and to allow Spanish speaking participants the option to complete the survey questions on paper independently.	

Version Date: from 6/25/2020 to 3/31/2021

Section(s)	Description of Change
1.2 Schema 5.8 Registration and Randomization	Removed "after 1st fraction of brachytherapy" from the randomization time limit. The randomization timeframe is "10 days prior to 2nd fraction"

9.2 Randomization and stratification	
Rationale: For flexibility as there is no statistical reason to limit randomization to after the first brachytherapy.	
5.1 Inclusion Criteria 5.2 Exclusion Criteria	Updated Inclusion criteria 2 and exclusion criteria 1 & 3 to clarify that radiation therapy that is a part of the patient's current definitive treatment plan for the cancer of interest is acceptable
Rationale: It is common for the study's patient population to receive a combination of EBRT, brachytherapy and chemotherapy as definitive treatment. The intent is to not exclude individuals receiving other therapies that are a part of their current treatment plan for cervical cancer.	
Abbreviations 5.1 Inclusion Criteria 8.1.1 Physical Exam	Changed KPS to KPS or ECOG
Rationale: For flexibility based on standard practice	
5.5 Description of Study intervention	Added a description of the Arm assignments and details about fraction 1.
Rationale: To provide additional clarity on the assignments and to align this section with section 4.1	
6.3 Product Storage and Stability	Added "after manufacture"
Rationale: For additional clarity on the expiration of the device.	
5.8 Registration and Randomization	Added statement "eligibility and registration can occur after 1st fraction but before 2nd fraction"
Rationale: The first fraction is considered a "screening procedure" and the second is considered the start of treatment. Eligibility confirmation and registration do not need to occur before the first fraction.	
7.2 Participant reported outcomes 7.3 Physicist and Physician reported outcomes 9.3.2 Study Outcomes & Endpoints	Added "both standard and BrachyGel" Reworded "period" to "fraction 2-5" Added statement about only dosimetry measurements data will be collected from Fraction 1 Added statement that sedated patients will not be asked the patient survey questions
Rationale: Patient and doctor/physicist surveys only need to be completed starting at fraction 2 since fraction 2 is considered the start of treatment. Fraction 1 is considered a part of "screening" and the dosimetry values collected will be used as baseline values per section 9.1. Since the participant reported outcomes are exploratory, sedated patients can still be enrolled as data for the primary endpoints can still be collected.	
8.1.4 Abnormal Laboratory Values 8.1.5 Time Period & Frequency for Event Assessment & Follow up	Reworded to state that Abnormal laboratory values will not be considered AEs and will not be recorded or reported
Rationale: Lab values are not being collected or assessed for the study. Lab values are typically not collected for brachytherapy as SOC.	
10.1.2 Consent Procedures and Documentation	Added verbal consenting information for doctors and physicists
Rationale: Doctors and physicists who plan to complete the Physician and Physicist Assessment Surveys are considered participants. Verbal informed consent needs to be obtained	
11.2.1 Data Collection and Management Responsibilities	Removed references to Oncore as the eCRF system
Rationale: Oncore is no longer the primary system being used for IIT eCRFs	

11.4 Conflict of Interest Policy	Dr. Showalter was shifted from Medical Monitor to Sub-Investigator
Rationale: Consistency with his corrected role	
12.1 Schedule of Events	Footnotes 4-6 were added and Footnote 3 updated to account for sedated patients
Rationale: To align with the changes made throughout the document	
12.1 Schedule of Events	Concomitant medication review removed from Brachytherapy 1
Rationale: Patients are always sedated for Brachytherapy 1 therefore not pain control medications would be administered during the procedure.	
12.1 Schedule of Events	Added a +/- 2 week window to the 30 day safety follow up
Rationale: For flexibility and clarity to account for changes in patient scheduling.	
12.2 Physicist/Dosimetrist CRF 12.4 Physician CRF	Reworded "circling" to "clearly selecting" in all of the survey questions
Rationale: To allow electronic completion of CRFs	
Abbreviation Table 5.8 Registration and Randomization 8.1.6 AE Reporting 10.1.3 Confidentially & Privacy	Reworded "Oncore" references to " designated EDC system"
Rationale: Oncore is no longer the exclusive data entry system for the study.	
8.1.5 Time Period & Frequency for Event Assessment & Follow up 12.1 Schedule of Events	Updated start of AE recording and reporting from time "informed consent was obtained" to "after the completion of the brachytherapy fraction 2"
Rationale: Brachytherapy 2 is considered the start of treatment. The time in between informed consent and Brachytherapy 2 is considered screening. All abnormalities occurring during that timeframe are considered baseline conditions.	
9.4 Sample size and Accrual	Updated the patient and oncologist/physicist accrual goals.
Rationale: Added for clarity	
5.1 Inclusion Criteria	Removed Inclusion criteria #4 " ability to read and write English or Spanish"
Rationale: Patient participants do not need to read or write for the study since the patient comfort survey is verbally presented to the patient. Any non-English speaking patient can enroll as long as the patient can be properly consented and there is an acceptable interpreter for the subject's native language.	
9.7.2 Protocol Exceptions	Added section and definition
Rationale: Inadvertently omitted from previous versions. This section is applicable since this is a multisite study.	

Version Date: 25 June 2020

Section(s)	Description of Change

Key Roles and Study Governance	Dr. Showalter was shifted from Medical Monitor to Sub-Investigator
Rationale: Dr. Showalter needs to be able to participate as a sub-investigator in order to perform brachytherapy and cannot serve as both the medical monitor AND a co-investigator.	
1.1 Synopsis 5.1 Inclusion Criteria	Expanded the range of stages to include IB1 and IVB
Rationale: While uncommon, patients with these stages of disease may receive brachytherapy as definitive treatment for cervical cancer and there is no reason to exclude them from participation	
6.5 Concomitant Therapy	Changed “during the procedure” to “for the procedure”
Rationale: In some cases pain medication for the procedure may be given prior to the procedure or just following, and this should also be captured.	
13.1 Schedule of Activities (SOA)	“Medical History” was updated to “Baseline conditions/assessment”
Rationale: A true history is not necessary, but an assessment of baseline conditions is required in order to assess adverse events	