PROTOCOL TITLE

Vaginal Effects after Radiation Therapy in Anal Cancer Study (VERITAS)

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1. SUMMARY OF TRIAL

This is a prospective single arm study.

Hypothesis
Primary hypothesis is that patients are able to comply with the use of vaginal dilators after radical chemoradiation for anal cancer.
Secondary hypotheses include that the use of vaginal dilators reduces grade 3-4 vaginal toxicity (stenosis), and therefore improves vaginal health, sexual function and quality of life.

Inclusion Criteria
Inclusion criteria are age greater than 18 years, female, histologically-proven non distant metastatic anal cancer (squamous cell carcinoma or adenocarcinoma), suitable for treatment with radical pelvic radiotherapy to greater than 45 Gray with or without concurrent chemotherapy (Mitomycin C (MMC) and/or 5-Fluorouracil (5FU).

Exclusion Criteria
Participants with pre-existing psychiatric illness or who had abdominoperineal resection are excluded.

Radiation Therapy Treatment
The standard regimen consist of external beam radiotherapy to a total dose of 50.4 to 54Gy using a three-phase technique. From 2011, some participants are treated with a two-phase Intensity Modulated Radiotherapy Technique (IMRT).

Chemotherapy Treatment
Standard concurrent chemotherapy consists of infusional 5FU 1g/m^2 for 4 days in week 1 and 5, with MMC 10mg/m^2 on day 1. Some participants will receive protracted infusional 5FU (PVI 5FU) 300mg/m^2 for 96 hours each week.

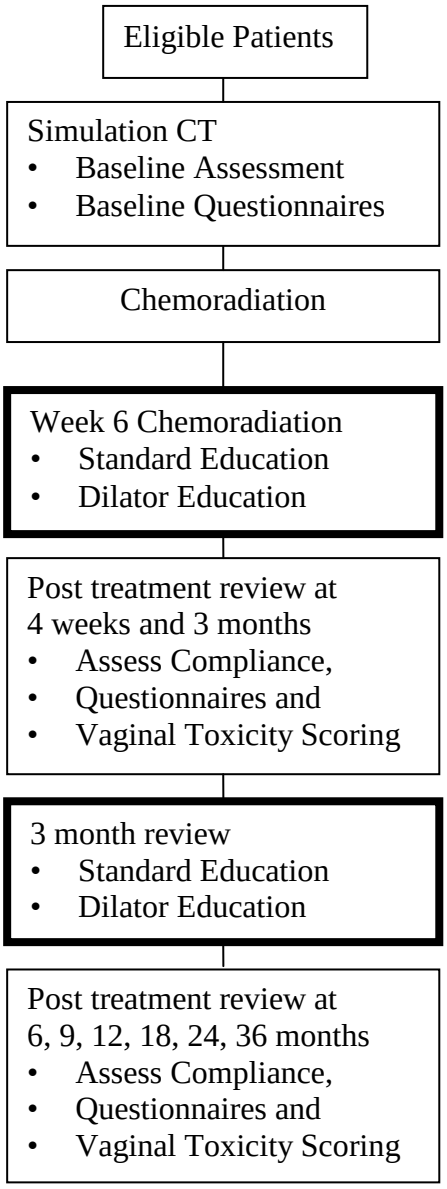
Device
Vaginal dilators are smooth rigid cylinder-shaped pieces of plastic. There are four standard sizes of varying diameters. They are used with a lubricant or oestrogen cream. Standard

recommendation for their use: initiate insertion within 6 weeks of completing chemoradiation; insert 3 times per week for 5 minutes duration.

Follow-up Schedule
At the completion of chemoradiation, participants will be reviewed at 4 weeks; and 3, 6, 9, 12, 18, 24 and 36 months.

Sample Size and Duration
A pragmatic sample size of forty participants will be accrued for this trial. The anticipated duration to complete accrual is 30 months. Participants will undergo 6 weeks of chemoradiation and then 3 years follow up. The total study duration is therefore expected to be 68 months. A planned interim analysis will take place after 15 participants have completed 12 months follow up.

2. STUDY SCHEMA



Standard Education comprises verbal and written information regarding the side effects of pelvic radiation.

Dilator Education comprises verbal and written information regarding standard recommendation for their use: initiate insertion within 6 weeks of completing chemoradiation; insert 3 times per week for 5 minutes duration. They are used with lubricant or oestrogen cream.

3. BACKGROUND

Rationale for the Study

Chemoradiation is a very effective organ-sparing treatment approach for anal cancer. A retrospective analysis of 284 patients from our institution suggests good outcomes and long term survival. Female genital toxicity and insufficiency fractures were identified as two predominant late effects in post-menopausal women. While bone toxicity attributed to radiotherapy is recognised and well documented, vaginal toxicity is underreported and scarcely documented (1).

To date there is no data on vaginal effects after radiation therapy in anal cancer patients. Existing literature on vaginal toxicities are based on gynae-oncology treatments involving brachytherapy and surgery. Many existing studies have poor research methodology because scientific evaluation of the vagina is difficult. Vaginal dilators are commonly recommended in gynae-oncology patients to reduce vaginal toxicities after chemoradiation. But there is weak and conflicting evidence regarding the efficacy of vaginal dilators in preventing vaginal stenosis. For anal cancer patients, quality of life is an important aspect of treatment outcomes because of high survival rates and organ preservation. Quality of life studies in these patients have shown acceptable overall quality of life scores, but sexual dysfunction is prominent amongst survivors.

The primary objective of this study is to assess compliance of vaginal dilator use after chemoradiation for anal cancer. The secondary objective is to assess the effect of vaginal dilator use on reducing vaginal toxicity (stenosis). An exploratory objective is set to assess the impact of vaginal dilator use on quality of life and sexual function.

Vaginal Dilators

Vaginal dilators have become an accepted intervention based on Grade 2C evidence presented in Cochrane Review 2003 (2). In theory, it prevents vaginal stenosis by breaking down adhesions and promote vaginal stretching (3). In 2007, a study of 100 women from Tata Hospital, Mumbai found statistically significant increment in vaginal length with dilator use at 6 weeks to 4 months with further minimal benefit beyond 4 months (4). Other studies have identified consistent issues of poor compliance with dilator use and lack of dilator education (5-7). Provision of dedicated patient education materials containing concrete objective information and psychoeducation may be effective strategies to improve patient compliance (6, 8-9).

Internationally, dilator use is routinely advocated in 97% of centres in United Kingdom. In stark contrast, it is not promoted at all in United States of America although doctors may advise patients to do so. In Australia, dilator use is less protocol driven and often dominated by non-scientific opinion of leading clinicians. In a survey of 15 Australian brachytherapy

centres in 2004, only 8 centres routinely provided dilators to all gynae-oncology patients. The authors recommend commencing dilator use within 4 weeks of completing chemoradiation. Whilst there is no conclusive evidence for specific frequency, duration of insertion or long term use, patients should be encouraged to use it daily or at least 2-3 times per week for a minimum of 3 years or indefinitely (3).

The Cochrane Review 2010 presented conflicting data. It suggested that routine dilatation during or soon after radiation can be harmful and there is no reliable data to demonstrate prevention of vaginal stenosis or improvement in quality of life with dilator use (10).

Vaginal Toxicity

The pathogenesis of vaginal toxicity from pelvic radiotherapy is two-fold. Loss of ovarian function results in hormone deprivation (11). Local effects of radiation on the vagina result in mucosal damage, loss of lubrication, tissue agglutination, ulceration and stenosis (12-13). Vaginal elasticity is compromised (8, 14).

In gynae-oncology, small retrospective studies have implicated brachytherapy treatment and more advanced disease as predisposing factors for vaginal stenosis but statistically sound conclusions are lacking (8, 15).

There is no consensus definition of vaginal stenosis (2). Stenosis can be defined by the “two finger test” which evaluates changes in diameter (16), length less than 8 cm (14) or by examination findings of stenosis in the upper 1/3 or lower 2/3 (15).

The onset of vaginal stenosis after brachytherapy can be as early as four weeks or up to 3 months. Time taken to establish stenosis has been reported as 7.5 months, up to 3 years and one study suggest continuing stenosis up to 5 years (17-19).

Vaginal Toxicity and Quality of Life (QOL) Assessments

Several validated assessment tools for vaginal toxicity exist. The Franco-Italian Scoring system was first developed in 1993 and has since been found to correlate well with the LENT/SOMA and RTOG/EORTC systems in 2008 (20-21). The CTCAE v 4.03 (22) is widely utilized in clinical trials and offers a comprehensive scoring system which is specific for all aspects of vaginal toxicity.

Specific quality of life assessment tools are lacking for this purpose. The first QOL assessment of anal cancer patients treated with chemoradiation was reported in 1999 (23). It utilized the EORTC QLQ-C30 and EORTC QLQ-CR38 questionnaires (24). However, the colorectal site-specific CR38 module is not applicable to healthy non-cancer control group hence the baseline comparisons to the general population cannot be validated. Since then, it has been superseded by the anorectal site-specific module CR29.

More recent studies have utilized the FACT-C and MOS Sexual Problem Scale (25) and EORTC-QLQ CR29 Questionnaire (26). The Female Sexual Function Index Tool which was developed by Rosen et al (27) for CRC cancer survivors is chosen for this study for various reasons. It is a 19 item self-reported, gender-specific questionnaire which encompasses the multidimensional nature of sexual dysfunction. Six domains of sexual function are assessed: Desire, arousal, lubrication, orgasmic capacity, dyspareunia and sexual satisfaction. Normative data is available for baseline comparisons to the general population. It is psychometrically sound and has been validated by Wiegel et al (28).

Device
Vaginal dilators are smooth rigid cylinder-shaped pieces of plastic made of Delrin® acetal homopolymer. They are manufactured at the Department of Radiation Engineering, Peter MacCallum Cancer Centre.

Delrin® is a crystalline plastic that offers an excellent balance of properties that bridge the gap between metals and plastics. It possess high tensile strength, creep resistance, toughness and exhibits low moisture absorption. Four standard sizes are available.

Side Effects of Device
In general, there are no anticipated serious adverse events associated with dilator use. Patients can expect minor discomfort. However, there is potential for psychological stress associated with this practice. It is possible that physical trauma and the resultant healing process may accelerate fibrosis during radiotherapy. Hence, the Cochrane Review 2010 does not recommend dilator use during or immediately after radiation (10). There is one case report of dilator use causing recto-vaginal fistula (29).

Ethical Standard
This trial will be conducted in compliance with the protocol according to the good clinical practice guideline requirements as per the National Statement on Ethical Conduct in Human Research 2007 and ICH-Good Clinical Practice (GCP).

4. TRIAL OBJECTIVES and PURPOSE

Primary Objective

To assess compliance of vaginal dilator use after chemoradiation for anal cancer

Secondary Objective

To assess the effect of vaginal dilator use on vaginal toxicity

Exploratory/ Tertiary Objective

To investigate the impact of vaginal dilator use on QOL and sexual function

5. TRIAL DESIGN AND ENDPOINT DEFINITIONS

This is a single institution (including satellite centres) prospective single arm study.

Trial Design

Total Participant Accrual
Forty participants will be accrued for this trial.

Duration of Study
The anticipated duration to complete accrual is 30 months. Participants will undergo 6 weeks of chemoradiation and then 3 years follow up. The total study duration is therefore expected to be 68 months. A planned interim analysis will take place after 15 participants have completed 12 months follow up.

Treatment Sequencing
All participants will undergo standard chemoradiation over 6 weeks. They will receive education by verbal counselling and written information regarding the side effects of pelvic radiotherapy and vaginal dilator use. This will be conducted in the last week of chemoradiation (i.e. week 6) and repeated at the 3-month review.

Participants will be followed up at 4 weeks; and 3, 6, 9, 12, 18, 24 and 36 months after treatment. At each review session, compliance with vaginal dilator use, vaginal examinations for toxicity scoring, and quality of life questionnaires will be completed and documented.

Participant Education
Standard education will comprise of verbal and written information regarding the side effects of pelvic radiation (see appendix). Permission for sexual intercourse is given to participants and frequency is documented. All participants will complete a supportive care screening tool.

Standard recommendation for vaginal dilator use: initiate vaginal dilator insertion within 6 weeks of completing chemoradiation, insert 3 times per week for 5 minutes duration, as tolerated.

Radiotherapy Schedule
Standard chemoradiation to 54 Gy in 30 fractions, 5 fractions per week using a three phase 3D-conformal technique.

From 2011, all participants except staged T1N0M0 are treated with a two-phase IMRT technique using simultaneous integrated boost.

Chemotherapy Schedule
Standard concurrent chemotherapy consists of infusional 5FU in week 1 and 5, with MMC on day 1. Some participants will receive PVI 5FU for 96 hours each week.

Vaginal Dilator
Vaginal dilators are smooth rigid cylinder-shaped pieces of plastic made of Delrin® acetal homopolymer.

Vaginal Dilator Therapy
Vaginal dilators are used with lubricant or oestrogen cream. Standard recommendation for vaginal dilator use: initiate vaginal dilator insertion within 6 weeks of completing chemoradiation, insert 3 times per week for 5 minutes duration, as tolerated. Permission for sexual intercourse up to 3 times per week is given to all participants.

Primary Endpoints: Compliance

Overall compliance: Adherence to the recommended dilator regimen (Yes or No) as defined by satisfying any three of the following four criteria:

- Commence dilator use within 6 weeks of completing chemoradiation
- A combined average frequency of dilator use and/or sexual intercourse of at least 3 times per week
- An average insertion duration of at least 5 minutes
- A duration of use of at least 12 months

Information regarding the following individual components of dilator use and sexual intercourse will be collected at baseline and at each of the follow-up reviews in order to determine the primary endpoint of overall compliance:

- Time between completion of chemoradiation to initiation of dilator use (days/weeks) (<4 weeks, 4 – 6 weeks, 6 – 12 weeks, >12 weeks)
- Average frequency of use (times per week) (<2, 2 – 3, >3 times per week)
- Average duration of insertion (minutes) (<5, 5 – 10, >10 minutes)
- Duration of dilator use (weeks/months/years) (6 weeks, 3, 6, 9, 12 months, 1 – 3 years, indefinitely)
- Average frequency of sexual intercourse (times per week)

Secondary Endpoints: Vaginal Toxicity

Incidence of stenosis as defined by grade 3+ vaginal stricture per CTCAE version 4.03
Time from date of registration until onset of stenosis (in weeks) where the date of onset of stenosis is defined to be the date of the earliest review where grade 3+ vaginal stricture is reported.
Severity of stenosis as defined by CTCAE version 4.03

Exploratory/ Tertiary Endpoints: Vaginal Health and QOL

Six important domain scores (desire, arousal, lubrication, orgasm, satisfaction, pain) assessed using The Female Sexual Function Index (FSFI): A Multidimensional Self-Report Instrument for the Assessment of Female Sexual Function (27).

6. SELECTION AND WITHDRAWAL OF SUBJECTS

Nurse coordinators, radiotherapy nursing staff, or treating radiation oncologists, medical oncologists or surgeons will identify eligible patients according to the inclusion and exclusion criteria. Eligible patients will be approached and written consent obtained. The trial site research coordinator, nurse coordinators or radiotherapy nursing staff will be notified.

Inclusion Criteria

Age 18 years or older
Has provided written informed consent for participation in this trial (see appendices)
Histological or cytologically confirmed anal cancer (all histological types) *
Non-distant metastatic anal cancer
ECOG performance status score of 2 or less (see appendix 1)
Suitable for radical pelvic radiotherapy plus or minus concurrent chemotherapy
Available for follow up

**NOTE - Patients without histologically or cytologically confirmed anal cancer will still be considered eligible for study entry if a consensus diagnosis of anal cancer has been made based on; a) surgical impression (at colonoscopy and/or EUA) and/or a positive PET scan (i.e. FDG activity in the anal canal) and b) if there is an intention to treat with curative chemo-radiotherapy*.

Exclusion Criteria

Intended to received less than 45 Gy to pelvis i.e. not radical dose

Participants who had or will require abdominoperineal resection due to changes in vaginal anatomy
Significant psychiatric condition receiving active management which interferes with ability to comply with vaginal dilator use due to psychological reasons.

Early termination/Deviations/Withdrawals

If a participant develops severe vaginal stenosis at 6 months after chemoradiation

- Use of vaginal dilators will not be recommended aggressively due to lack of definitive evidence on efficacy of dilators in treating stenosis.
- Action: to repeat standard education
- Give permission for sexual intercourse up to 3 times per week
- Utilise the PLISSIT model framework to discuss sexuality with cancer participants (see appendix 2)
- Referral to psychologist and/or gynaecologist

Slow accrual: Early termination of the trial will be considered if after 15 months, the number of patients accrued to the trial is no greater than 10.

A trial participant may discontinue trial treatment for any of the following reasons:

- Disease progression or new pelvic malignancy requiring further treatment
- Unacceptable toxicity e.g. severe vaginal stenosis at 6 months
- Intercurrent illness which prevents completion of chemoradiation or vaginal dilator use.
- Withdrawal of consent for treatment by participant
- Any alterations in the participant's condition which justifies the discontinuation of treatment in the investigator's opinion

Discontinuation of treatment does not necessarily indicate withdrawal from the trial. The distinction between discontinuation of treatment and withdrawal from the trial is shown by the definitions in the following subsections.

Protocol Treatment Discontinuation

A participant would be considered to have discontinued treatment where trial related treatment is ceased according to the reason(s) outlined above. The participant may however still agree to further follow-up assessments.

The participants' discontinuation of treatment must be documented in the medical records (i.e. source documents) and transcribed onto the relevant CRF.

Withdrawal from Trial

Trial Participants have the option to completely withdraw from the trial at any time without giving a reason.

Total withdrawal would occur in the circumstance that the participant decides to completely withdraw from all treatment aspects of the trial, and does not agree to any further scheduled follow up assessments. The participants' total withdrawal must be documented in the medical

records and transcribed onto the relevant CRF. No further information will be collected from this participant for the purpose of this trial.

7. TREATMENT OF SUBJECTS

Radiotherapy Schedule

This component will be supervised by radiation oncologists.

Phase 1
Parallel-opposed anterior and posterior fields to a dose of 36 Gy in 20 fractions. The superior field border is 1 cm above the inferior sacroiliac joints or 5 cm proximal to the primary tumour, whichever is more proximal. The lateral borders are at the lateral acetabulum (if inguinal nodes are negative) or the anterior superior iliac spine (if inguinal nodes are positive). The inferior border is 3 cm below the primary tumour.

Phase 2
A three-field technique with posterior, left lateral and right lateral beams to a dose of 45 Gy in 25 fractions. The superior and inferior borders are as for Phase 1, with lateral borders 2 cm beyond the pelvic brim, the anterior border 3 cm anterior to the primary tumour, and the posterior border 2 cm posterior to the anterior sacral margin.

Phase 3
A three-field technique to boost the anal canal and primary tumour with a 3 cm margin to a total dose of 50.4 to 54 Gy. Involved inguinal nodes are boosted to the same dose as the primary site using electron fields. In participants with Stage I disease, elective inguinal irradiation is omitted, and a two-phase technique using posterior, left lateral and right lateral beams are used throughout the treatment.

From 2011, all participants except staged T1N0M0 are treated with a two-phase IMRT technique using simultaneous integrated boost. A dose of 45Gy is delivered to the pelvic and inguinal nodal volumes and 54-60Gy to the gross disease. CTV & PTV volumes for IMRT will be contoured as per the Gastrointestinal Unit's contouring guidelines for anal canal cancer.

Chemotherapy Schedule

This component will be supervised by medical oncologists.
Standard concurrent chemotherapy consist of infusional 5-Fluorouracil (5FU) 1g/m^2 for 4 days in week 1 and 5, with Mitomycin-C (MMC) 10mg/m^2 on day 1. Some participants will receive protracted infusional 5FU (PVI 5FU) 300mg/m2 for 96 hours each week.

Vaginal Dilator Therapy

This component will be supervised by trial site nurse coordinators or radiotherapy nursing staff.

Vaginal dilators are used with lubricant or oestrogen cream. Standard recommendation for use: initiate insertion within 6 weeks of completing chemoradiation; insert 3 times per week for 5 minutes duration. Permission for sexual intercourse is given to ALL participants and frequency is documented.

Standard education comprises verbal and written information regarding the side effects of pelvic radiation.

All participants are required to complete a supportive care screening tool.

The four standard sizes and associated costs are:

Size	Diameter (mm)	Material cost AUD (each)
Extra Small	18	$1.20
Small	22	$2.20
Medium	28.5	$3.20
Large	35	$4.20

8. STUDY PROCEDURES AND ASSESSMENT SCHEDULE

Methods and timing for assessing, recording, and analysing of efficacy parameters.

The following assessments will occur during the trial. A table of assessments is provided in the appendices.
Reviews conducted at baseline, 4 weeks; and 3, 6, 9, 12, 18, 24 and 36 months post completion of chemoradiation.

Pre-Registration Assessments

The following assessments must be performed within 8 weeks prior to registration.
Registration of the participant should occur between date of simulation CT and expected start date of chemoradiation.

These assessments must be conducted prior to registration.

- Documentation confirming participant eligibility e.g. inclusion criteria
- Histology report
- Stage
- Diagnostic imaging – CT Chest Abdomen Pelvis and/or PET scan and/or MRI scan
- Physical examination
-
- Menopausal status
- Sexually active status

Pre-Treatment Assessments

The following tests must be performed within 15 weeks of commencement of protocol treatment. Baseline assessments have to be done prior to commencement of chemoradiation. Chemoradiation is expected to be at least 6 weeks duration and up to 8 weeks duration if a treatment break is clinically indicated. Protocol treatment should commence within 4-6 weeks after completion of chemoradiation.

These assessments must be conducted between registration and commencement of chemoradiation.

- ECOG performance status

- Vaginal health
- CTCAE (see Appendix 5)
- Premorbid sexual health
- FSFI Questionnaire
- Impact of presenting symptoms and diagnosis

  E.g. Pain, bleeding, fatigue, stress, anxiety, loss of libido

Treatment Assessments

During treatment, there will be no additional assessments for trial purposes.

Follow-up Assessments

The following assessments will occur at 4 weeks; and 3, 6, 9, 12, 18, 24, 36 months from the date of completion of chemoradiation. At each review the following assessments are performed:

- ECOG performance status
- Vaginal health
- Toxicity scoring CTCAE
- Document compliance to recommended regimen
- Time to initiate
- Frequency including frequency of sexual intercourse
- Duration of insertion
- Duration of use
- Sexual health
- FSFI Questionnaire

9. ASSESSMENT OF SAFETY

It is important that Adverse Events (AEs) are monitored in the interest of participant safety. The investigator at each trial site is responsible for assessing and reporting AEs as part of routine clinical care and data collection. A subset of AEs will be classified as 'serious' and will require expedited reporting.

Adverse Event (AE)

An Adverse Event (AE) is any untoward medical occurrence in a participant or clinical investigation subject administered a pharmaceutical product (or any other protocol specified intervention including radiation therapy, surgery or use of a device) and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign, symptom or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product (or associated with the use of any other protocol specified intervention including radiation therapy, surgery or use of a device).

Serious Adverse Event (SAE)

Serious Adverse Events require expedited reporting. SAEs are defined as any adverse event which:

- Results in death (i.e. fatal/grade 5 CTC AE)
- Is life-threatening (i.e. grade 4 CTC AE)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation*
- Results in persistent or significant disability/incapacity

Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was immediately at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.
*An event that results in hospitalisation or prolongs an existing hospitalisation will not be considered a serious adverse event if the only reason for the hospitalisation or prolongation was:

- administration of chemotherapy
- administration of trial procedures
- placement of a permanent intravenous catheter
- hospice placement for terminal care
- pre-trial scheduled elective surgery
- out-participant hospitalisation for procedures such as:
- Elective day surgery
- Convenience purposes (e.g. transportation difficulties)
- Planned admission as part of supportive care for insertion of PEG tube or naso-gastric tube for commencement of enteral feeding (i.e. did not occur following urgent admission as a result of weight loss or other participant medical events)

All protocol specified interventions (including pharmaceutical products, radiation therapy, surgery or use of a device) administered prior to the date of the event must be attributed a degree of causality from one of the following codes:

- Unrelated
- Unlikely to be related
- Possibly related
- Probably related
- Definitely related

Due to the similarity of protocol treatments to standard care, certain conditions/events defined as SAEs will be excluded from expedited reporting as SAEs:

- Progression of disease is not to be regarded as an SAE
- Death due to progressive disease is not to be regarded as an SAE
- Elective hospitalization and/or surgery for treatment of anal cancer or its complications
- Elective hospitalization to simplify treatment or study procedures
- Events that are unrelated to the study intervention (i.e the use of a vaginal dilator)

Methods and timing for assessing, recording, and analysing safety parameters.

In general, all expected and non-serious adverse events recorded during the course of the trial are to be amalgamated into a single report which is sent to the Trial Management Committee throughout the conduct of the trial and to BaCT at the time of interim analysis and at the conclusion of the trial. As the dilator intervention is being used for it's current TGAapproved indication there is no requirement for notification of the trial to the TGA through the Clinical Trial Notification Scheme. Appropriate scientific judgement should be applied for each situation. Examples of the type of information that may require reporting are;

- For an 'expected' serious adverse event, an increase in the rate of occurrence which is judged to be clinically important
- A significant hazard to the participant population such as lack of efficacy with a medicinal product used in treating life threatening disease.
- A major safety finding from a newly completed animal study (such as carcinogenicity).

The Investigator at the Trial Site is responsible for reporting Serious Adverse Events (SAEs) to the responsible HREC according to local requirements.

Other situations requiring expedited reporting

Overdoses
Overdoses (drug or radiation) must be reported to the DROCI Research Office, Research Manager if the event(s) associated with the overdose meet the SAE definitions. If no serious adverse events are experienced the overdose must be reported in the participants medical record and transcribed onto the relevant trial CRF.

Therapeutical Device Incidents
All serious and unexpected adverse device events, i.e. suspected problems with a therapeutic device which has or may present a health hazard (including deficiencies in labelling, instructions or packaging, defective components, performance failures, poor construction or design) must be reported to the Australian and New Zealand Medical Device Incident Report Investigation Scheme (IRIS) using the Medical Device Incident Report Form.

Serious Adverse Event Reporting

Trial Sites/Investigators
All SAEs that occur from the time a participant is registered on the Trial to within 30 days of the final protocol-specified treatment, intervention or procedure are required to be reported to the DROCI Research Office, Research Manager whether or not considered related to the treatment under investigation.

The Principal Investigator (PI) must:
Determine whether an AE is 'Serious' (refer to criteria).
For SAEs, the PI must then ascertain the suspected cause.
The attribution to the SAE must be recorded in the participants' medical records and reported on the SAE form.
The PI must then determine whether the SAE (or Serious Adverse Drug Reaction) is expected or unexpected.
Both expected and unexpected Serious Adverse Events and Serious Adverse Drug Reactions must be recorded in the participants' medical records and reported to the DROCI Research Office, Research Manager

Unexpected Serious Adverse Drug Reactions that are fatal or life threatening must be further reported to the TGA according to section below.

SAEs must be reported by completing the SAE form and FAXING it to the following:

Fax To:	Fax Number:
DROCI Research Office, Attention: Lisa Selbie	03 96560 1424

SAE forms are required at the following points:

Initial Report	Within one working day/24 hours of discovery or notification of the event. If the reporting of an SAE is delayed by more than 24 hours, an explanation must be provided in the comments section of the SAE form.
Incomplete Reports*	If all details are not available at the time of the initial report a completed report must be sent within the next 10 days.
Updated Report	If the event is not resolved (or is 'on-going') at the time of the initial report, the 'UPDATE: Outcome of Event' section' of the SAE Form must be completed and the form submitted to the DROCI Research Office, Research Manager as soon as the event is resolved (with or without sequelae) or if death has occurred.

*The Investigator is ultimately responsible for reporting the SAE and must sign the SAE report(s). Should this Investigator not be available to sign the initial SAE form within the 24 hour period, a comment to this effect must be written on the form and the form faxed without signature to the DROCI Research Office, Research Manager. The investigator must sign the SAE form as soon as possible and re-fax to the DROCI Research Office, Research Manager.

The Investigator at the Trial Site is responsible for determining the local SAE reporting requirements of the responsible HREC and subsequently notifying the HREC of SAEs as required.

All Serious Adverse Events (expected and unexpected) are required to be reported to the DROCI Research Office, Research Manager.

Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

All adverse events (including those that are non-serious or expected) which occur whilst the participant is enrolled on the trial must be reported in the participants' medical records and recorded on the relevant CRF. The Common Terminology Criteria for Adverse Events (CTCAE version 4.03 – see appendices) must be used to grade the severity of an event.

The type and duration of the follow-up of subjects after adverse events.

As per protocol or clinical indication

10. STATISTICS

Sample size calculation and precision

This study will aim to accrue a pragmatic sample size of 40 patients. It is expected that accrual will take approximately 30 months. It will therefore be possible to estimate the primary endpoint of overall compliance with a maximum 95% confidence interval width of +/- 17%.

The table below provides a summary of the resulting 95% confidence intervals for a range of different estimates of the percentage of patients satisfying the criteria of overall compliance with recommended dilator use.

Percentage of patients satisfying the criteria of overall compliance with the recommendations for dilator use	95% CI
0/40 = 0%	(0.0%, 7.8%)
4/40 = 10%	(3.5%, 22.7%)
8/40 = 20%	(9.4%, 34.4%)
12/40 = 30%	(16.6%, 45.8%)
16/40 = 40%	(25.8%, 56.7%)
20/40 = 50%	(34.4%, 65.6%)
24/40 = 60%	(43.3%, 74.2%)
28/40 = 70%	(54.2%, 83.4%)
32/40 = 80%	(65.6%, 90.6%)
36/40 = 90%	(77.3%, 96.5%)
40/40 = 100%	(92.2%, 100.0%)

This sample size is considered large enough to provide a useful first estimate with an acceptable level of precision for the compliance with recommended dilator use after chemoradiation for anal cancer.

Statistical methods

All patients registered on the study will be accounted for in reports of study outcomes. A final analysis of all primary, secondary and exploratory endpoints will be performed at the end of the study, when all patients have been followed for 3 years. A planned interim analysis of all study endpoints will also take place when 15 patients have been recruited to the study, undergone chemoradiation and completed a minimum of 12 months follow-up. This interim analysis will not be performed with the aim of stopping the trial early due to efficacy or futility, but simply to provide a first look at data from a study in a novel area of research.

Descriptive statistics of characteristics measured at baseline for all patients registered will be reported: as number of patients, mean, median, minimum and maximum for continuous variables, and as counts and percentages for categorical variables.

In order to address the primary objective, the proportion of patients satisfying the criteria for overall compliance with the recommended dilator regimen will be calculated with an accompanying two-sided 95% confidence interval based on exact values of the binomial distribution. The standard and dilator education package will be deemed effective for patients undergoing chemotherapy for anal cancer if the observed rate of overall compliance is at least 70%.

The individual component measures of compliance such as time to initiate use, average frequency and duration of use, and average frequency of sexual intercourse will be summarised descriptively for each follow-up review at 4 weeks; and 3, 6, 9, 12, 18, 24 and 36

months post completion of chemoradiation. If the rate of compliance is high enough, it may be possible to investigate the association of patient characteristics with the likelihood of compliance using binary logistic regression.

Very few patients are expected to withdraw from the study early due to progression, death, severe toxicity, withdrawal of consent or loss to follow-up as the study follow-up reviews are scheduled to coincide with usual oncology follow-up appointments; those patients who withdraw prior to the 12 month follow-up review will not be evaluable for the primary endpoint of overall compliance. Analysis of the individual component measures of compliance at each of the follow-up review time points will include all patients still enrolled in the study at the time of the review.

In order to address the secondary objective, the incidence and severity of stenosis will be summarised using frequencies and percentages of the CTCAE version 4.03 grades at each follow-up review. The association between the individual component measures of compliance and the incidence of at least one episode of stenosis as measured by grade 3+ vaginal stricture at each review time point will be assessed using Fisher's exact test. The time until onset of stenosis will be described for the whole cohort using standard survival analysis techniques, including Kaplan-Meier survival curves and the log-rank test. The prognostic value of patient baseline characteristics may also be investigated using Cox proportional hazards regression.

The six FSFI QOL domains of interest will initially be summarised descriptively at baseline and at each follow-up review for the sample as a whole. It will also be possible to investigate associations with the individual component measures of compliance at each time point separately by comparing mean QOL scores using independent two-sample t-tests. Overall patterns of change in sexual function across the entire study duration may also be investigated using general linear mixed modelling. Adherence to model assumptions will be assessed in each instance and alternative approaches such as transformations or non-parametric methods will be considered where appropriate.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Peter MacCallum Cancer Centre will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

12. ETHICS

Ethical Principles and Regulatory Compliance

The trial will be conducted according to the following regulations and guidelines:

National Statement on Ethical Conduct in Human Research, (Australia, 2007)
Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Australia, July 2000)
The Australian Code for Responsible Conduct of Research (August 2007)
Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (last amended by the World Medical Association, 2008)

This Protocol, including the Participant information Sheet and Consent Form (PIC) has been approved by the Peter MacCallum Ethics Committee before enrolment of trial participants.

Adherence to Protocol

Except for an emergency situation in which proper care for the protection, safety and well being of the trial participant requires that an alternative treatment be used, the trial shall be conducted exactly as described in the approved protocol. Any deviation from the protocol must be recorded and explained.

Informed Consent

The Principal Investigator is responsible for ensuring that written Informed Consent is obtained from trial participants before trial entry.

Confidentiality

The trial will be conducted in accordance with applicable Privacy Acts and Regulations. All information regarding trial participants must be treated in strict confidence. Data, which identify any trial participant, must not be revealed to anyone not directly involved in the trial or the clinical care of that participant. An exception is where the trial participant has provided written consent for his/her records to be included in source document verification. In this instance, the records may be inspected by (a) a representative of TROG for the purposes of source document verification or quality audit as stipulated in the ICH GCP Guidelines, or (b) a representative of a government regulatory authority for the purposes of official inspection. Records must be made available for inspection on the understanding that all information relating to trial participants will be treated in strict professional confidence.

13. DATA HANDLING AND RECORD KEEPING

CRFs will be supplied by the Trial Management Centre, DROCI Research Office (East Melbourne). Trial Site Coordinators (Moorabbin, Box Hill, Sunshine, Bendigo), and Principal Investigators (and/or Sub-investigators) at participating Trial Sites must transcribe source data from the source documents onto the CRFs as soon as they are collected.

Completed original CRFs should be returned to the Trial Management Centre, DROCI Research Office at times requested (refer to CRFs) and a copy of each CRF should be kept at the Trial Site.

Trial Participants are to be identified by initials, trial registration number and Trial Site. All CRFs should be completed in black ink and never in pencil. All requested information must be entered on the CRFs. If an item is not available or is not applicable, this fact should be indicated; do not leave a space blank. A correction should be made by striking through the incorrect entry with a single line and by entering the correct information adjacent to it. The correction must be initialled and dated by an adequately qualified and authorised member of the research support team at the Trial Site.

The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

The Trial Site will prepare source documentation for QA reviews. Source data, including medical histories, radiological imaging, laboratory tests, chemotherapy and radiotherapy treatment records and verification films and portal images, must be retained for 15 years after completion of the trial and be available for checking or clarification of queries by the DROCI Research Office, Research Manager if required, in accordance with ICH GCP Guidelines.

Source data verification (SDV) will be performed as a minimum on patient eligibility criteria and the primary endpoint. SDV will be conducted by the DROCI Research Office independent of the Principal Investigator.

14. PUBLICATION POLICY

Results of the study will be published in a peer-reviewed journal.

15. REFERENCES

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Protocol Signatures

Version 3.1, 3 July 2012

Principal Investigator: Dr Jennifer Tan

Signature: _____ Date: ____ / ____/ ____

16. APPENDICES

Appendix 1

ECOG Performance Status Criteria

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

Appendix 2

PLISSIT & Ex-PLISSIT MODELS

PLISSIT Model: The PLISSIT Model (Permission, Limited Information, Specific Suggestions, and Intensive Therapy) is one of the most commonly used and effective models used for the assessment and intervention for sexual problems. Developed by Anon (1974), it helps streamline the assessment process.

The Ex-PLISSIT Model: The Ex-PLISSIT Model is an extension of the PLISSIT model. The additional features of the Ex-PLISSIT model include:

- explicit permission-giving at every stage (not just at the first stage)
- the need to review all interactions with patients
- challenging your own assumptions about the patient's situation. [1] [2]

The Ex-PLISSIT Model

Consider the example questions against each stage:

Stage	Description	Example
Permission	Give permission for the patient to have sexual feelings / relationships and normalise this.	Many women diagnosed with cancer find that it affects their relationships and their interest in sex. Is it ok if we discuss this issue?
Limited Information	Offer limited information to identify the effect of the cancer / treatment on sexuality. Correct any misconceptions, dispel myths, provide accurate information.	Treatment side-effects often have a big impact on sexual activities. You mentioned that you started having intercourse again, but that it's still painful after treatment. How is this pain affecting your sex life?
Specific Suggestions	Make specific suggestions to manage the sexual side-effects they've identified.	There are many ways couples can adapt their sex lives to adjust to the effect of the cancer and treatment. To address the issue of pain, consider which activities you can still enjoy when feeling sore from treatment. Focus on these instead of intercourse until you've recovered fully. How would you and your partner feel about focusing on other types of sexual activity?
Intensive Therapy	Identify further support for the issues you've discussed, and refer them if appropriate.	Some women find it helpful to get more support for the issues we've discussed. You mentioned you're feeling pressure to keep your sex life the way it's always been. It's making you very distressed, but you can't talk to your partner about it. Would you like to see a counsellor who's experienced in this area?

References

[1] From PLISSIT to Ex-PLISSIT
Editor: Davis S.
Authors: Davis S, Taylor B.
In: Google books - Rehabilitation: the use of theories and models in practice.
From: Edinburgh: Elsevier; 2006. p. 101–29.
[2] Using the extended PLISSIT model to address sexual healthcare needs
Authors: Taylor B, Davis S.
In: Nurs Stand 2006;21(11):35–40.
PLISSIT Training Module available from:
http://modules.cancerlearning.gov.au/psgc/images/stories/qut_gynae_3%20enquiringrespondiing_20110218.pdf

Appendix 3

TNM Staging for Anal Cancer

The anal canal extends from the rectum to the perianal skin and is lined by a mucous membrane that covers the internal sphincter. The following is a staging system for anal canal cancer that has been described by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer.Tumors of the anal margin (below the anal verge and involving the perianal hair-bearing skin) is classified with skin tumors.

The following is a staging system for anal canal cancer that has been described by the AJCC and the International Union Against Cancer.

Primary Tumor (T)[a]

TX	Primary tumor cannot be assessed.
T0	No evidence of primary tumor.
Tis	Carcinoma in situ (i.e., Bowen disease, high-grade squamous intraepithelial lesion, and anal intraepithelial neoplasia II–III.)
T1	Tumor ≤2 cm in greatest dimension.
T2	Tumor >2 cm but ≤5 cm in greatest dimension.
T3	Tumor >5 cm in greatest dimension.
T4	Tumor of any size invades adjacent organ(s), e.g., vagina, urethra, and bladder.[b]

[a]Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165-73.
[b]Direct invasion of the rectal wall, perirectal skin, subcutaneous tissue, or the sphincter muscle(s) is not classified as T4.

Regional Lymph Nodes (N)[a]

[a]Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165-73.	
NX	Regional lymph nodes cannot be assessed.
N0	No regional lymph node metastasis.
N1	Metastases in perirectal lymph node(s).
N2	Metastases in unilateral internal iliac and/or inguinal lymph node(s).
N3	Metastases in perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes.

Distant Metastasis (M)[a]

[a]Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165-73.	
M0	No distant metastasis.
M1	Distant metastasis.

Anatomic Stage/Prognostic Groups[a]

Stage	T	N	M
[a]Reprinted with permission from AJCC: Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 165-73.			
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
	T3	N0	M0
IIIA	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
	T4	N0	M0
IIIB	T4	N1	M0
	Any T	N2	M0
	Any T	N3	M0
IV	Any T	Any N	M1

References

Anus. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 167-169.

Appendix 4

Trial Flow Chart

		Post chemoradiation							
	Baseline	Week 4	3 month	6 month	9 month	12 month	18 month	24 month	36 month
Inclusion/ exclusion criteria	√								
Medical history	√								
Informed Consent	√								
physical examination incl vaginal	√	√	√	√	√	√	√	√	√
Vaginal CTCAE Scoring		√	√	√	√	√	√	√	√
ECOG performance	√	√	√	√	√	√	√	√	√
histology/pathology	√								
Stage TNM	√								
Diagnostic Imaging CT/PET/MRI	√								
Menopausal status	√	√	√	√	√	√	√	√	√
Sexually Active Status	√	√	√	√	√	√	√	√	√
Dilator Compliance – yes/no		√	√	√	√	√	√	√	√
Quality of life FSFI Questionnaire	√	√	√	√	√	√	√	√	√
Forms/ QA collection	√	√	√	√	√	√	√	√	√
CRF completion + submission	√	√	√	√	√	√	√	√	√
QA checklist completion	√				√				√

Appendix 5

CTCAE (Common Terminology Criteria for Adverse Events, V4.03)

Common Terminology Criteria for Adverse Events (CTCAE). National Cancer Institute, National Institutes of Health, U.S. Department of Health and Human Services; 2010 [cited 2010 June 14]; Version 4.03:

[Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Uterine fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the uterus and another organ or anatomic site.					
Uterine hemorrhage	Minimal bleeding identified on imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the uterus.					
Uterine obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of the uterine outlet.					
Uterine pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the uterus.					
Vaginal discharge	Mild vaginal discharge (greater than baseline for patient)	Moderate to heavy vaginal discharge; use of perineal pad or tampon indicated	-	-	-
Definition: A disorder characterized by vaginal secretions. Mucus produced by the cervical glands is discharged from the vagina naturally, especially during the childbearing years.					

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Vaginal pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-
Definition: A disorder characterized by a sensation of marked discomfort in the vagina.					
Vaginal perforation	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by a rupture in the vaginal wall.					
Vaginal stricture	Asymptomatic; mild vaginal shortening or narrowing	Vaginal narrowing and/or shortening not interfering with physical examination	Vaginal narrowing and/or shortening interfering with the use of tampons, sexual activity or physical examination	-	Death
Definition: A disorder characterized by a narrowing of the vaginal canal.					
Vaginismus	Mild discomfort or pain associated with vaginal spasm/tightening; no impact upon sexual function or physical examination	Moderate discomfort or pain associated with vaginal spasm/tightening; disruption in sexual function and physical examination	Severe discomfort or pain associated with vaginal spasm/tightening; unable to tolerate vaginal penetration or physical examination	-	-
Definition: A disorder characterized by involuntary spasms of the pelvic floor muscles, resulting in pathologic tightness of the vaginal wall during penetration such as during sexual intercourse.					

Reproductive system and breast disorders					
	Grade				
Adverse Event	1	2	3	4	5
Vaginal dryness	Mild vaginal dryness not interfering with sexual function	Moderate vaginal dryness interfering with sexual function or causing frequent discomfort	Severe vaginal dryness resulting in dyspareunia or severe discomfort	-	-
Definition: A disorder characterized by an uncomfortable feeling of itching and burning in the vagina.					
Vaginal fistula	Asymptomatic clinical or diagnostic observations only; intervention not indicated	Symptomatic and intervention not indicated	Severe symptoms; elective operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an abnormal communication between the vagina and another organ or anatomic site.					
Vaginal hemorrhage	Minimal bleeding identified on clinical exam or imaging study; intervention not indicated	Moderate bleeding; medical intervention indicated	Severe bleeding; transfusion indicated; radiologic or endoscopic intervention indicated	Life-threatening consequences; urgent operative intervention indicated	Death
Definition: A disorder characterized by bleeding from the vagina.					
Vaginal inflammation	Mild discomfort or pain, edema, or redness	Moderate discomfort or pain, edema, or redness; limiting instrumental ADL	Severe discomfort or pain, edema, or redness; limiting self care ADL; small areas of mucosal ulceration	Widespread areas of mucosal ulceration; life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by inflammation involving the vagina. Symptoms may include redness, edema, marked discomfort and an increase in vaginal discharge.					
Vaginal obstruction	Diagnostic observations only; intervention not indicated	Mild symptoms; elective intervention indicated	Severe symptoms; elective operative intervention indicated	-	-
Definition: A disorder characterized by blockage of vaginal canal.					

Appendix 6

FSFI Questionnaire

The Female Sexual Function Index (FSFI) assesses key dimensions of sexual function in adult women and identifies women at risk. FSFI is a brief and reliable tool to assess sexual functioning in women. It contains 19 questions across six domains—desire, arousal, lubrication, orgasm, satisfaction, and pain.

A sample question would be: “Over the past 4 weeks, how often did you feel sexual desire or interest?” The patient must give an answer ranging from 1 (almost never or never) to 5 (almost always or always).

Reference

Rosen R, Brown C, Heiman J, et al. The female sexual function index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. J Sex Marital Ther. 2000;26(2):181-208.

Question	Response Options
Q1: Over the past 4 weeks, how **often** did you feel sexual desire or interest?	5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q2: Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?	5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all
Q3. Over the past 4 weeks, how **often** did you feel sexually aroused ("turned on") during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q4. Over the past 4 weeks, how would you rate your **level** of sexual arousal ("turn on") during sexual activity or intercourse?	0 = No sexual activity 5 = Very high 4 = High 3 = Moderate 2 = Low 1 = Very low or none at all
Q5. Over the past 4 weeks, how **confident** were you about becoming sexually aroused during sexual activity or intercourse?	0 = No sexual activity 5 = Very high confidence 4 = High confidence 3 = Moderate confidence 2 = Low confidence 1 = Very low or no confidence
Q6. Over the past 4 weeks, how **often** have you been satisfied with your arousal (excitement) during sexual activity or intercourse? Response Options	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never

Q7: Over the past 4 weeks, how **often** did you become lubricated ("wet") during sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q8. Over the past 4 weeks, how **difficult** was it to become lubricated ("wet") during sexual activity or intercourse?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q9: Over the past 4 weeks, how often did you **maintain** your lubrication ("wetness") until completion of sexual activity or intercourse?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q10: Over the past 4 weeks, how **difficult** was it to maintain your lubrication ("wetness") until completion of sexual activity or intercourse?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q11. Over the past 4 weeks, when you had sexual stimulation or intercourse, how **often** did you reach orgasm (climax)?	0 = No sexual activity 5 = Almost always or always 4 = Most times (more than half the time) 3 = Sometimes (about half the time) 2 = A few times (less than half the time) 1 = Almost never or never
Q12: Over the past 4 weeks, when you had sexual stimulation or intercourse, how **difficult** was it for you to reach orgasm (climax)?	0 = No sexual activity 1 = Extremely difficult or impossible 2 = Very difficult 3 = Difficult 4 = Slightly difficult 5 = Not difficult
Q13: Over the past 4 weeks, how **satisfied** were you with your ability to reach orgasm (climax) during sexual activity or intercourse?	0 = No sexual activity 5 = Very satisfied 4 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
Q14: Over the past 4 weeks, how **satisfied** have you been with the amount of emotional closeness during sexual activity between you and your partner?	0 = No sexual activity 5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied

Q15: Over the past 4 weeks, how satisfied have you been with your sexual relationship with your partner?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
Q16: Over the past 4 weeks, how **satisfied** have you been with your overall sexual life?	5 = Very satisfied 4 = Moderately satisfied 3 = About equally satisfied and dissatisfied 2 = Moderately dissatisfied 1 = Very dissatisfied
Q17: Over the past 4 weeks, how **often** did you experience discomfort or pain during vaginal penetration?	0 = Did not attempt intercourse I = Almost always or always 2 = Most times (more than half the time) 3 = Sometimes (about half the time) 4 = A few times (less than half the time) 5 = Almost never or never
Q18: Over the past 4 weeks, how **often** did you experience discomfort or pain following vaginal penetration?	0 = Did not attempt intercourse 1 = Almost always or always 2 = Most times (more than half the time) 3 = Sometimes (about half the time) 4 = A few times (less than half the time) 5 = Almost never or never
Q19. Over the past 4 weeks, how would you rate your **level** (degree) of discomfort or pain during or following vaginal penetration?	0 = Did not attempt intercourse 1 = Very high 2 = High 3 = Moderate 4 = Low 5 = Very low or none at all

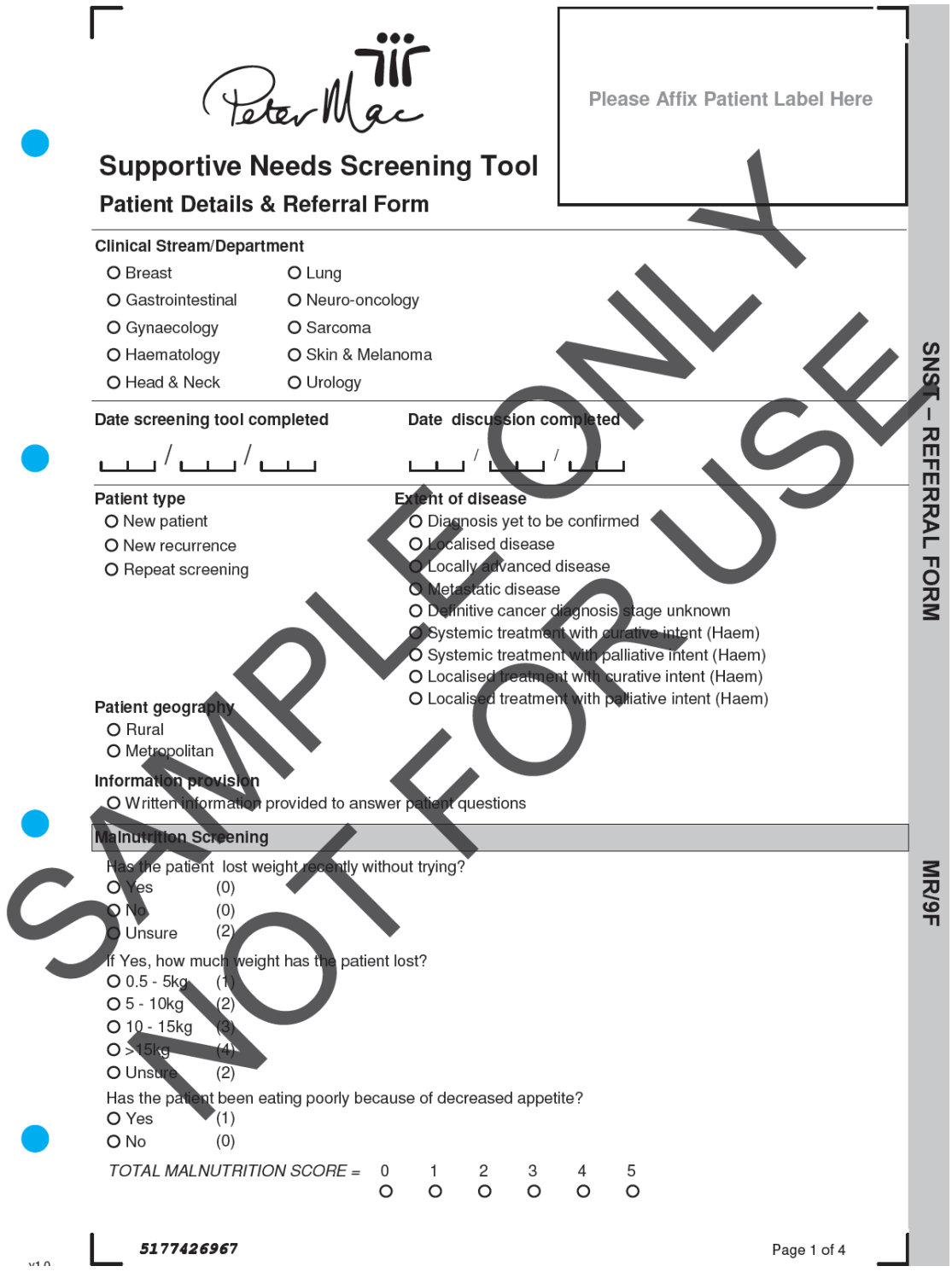
* For the complete FSFI questionnaire, instructions and scoring algorithm, please see www.FSFIquestionnaire.com, or contact Raymond Rosen Ph.D., (Department of Psychiatry: UMDNJ-Robert Wood Johnson Medical School, 675 Hoes Lane, Piscataway, NJ 08854)

The individual domain scores and full scale score of the FSFI are derived by the computational formula outlined in the table below. Individual domain scores are obtained by adding the scores of the individual items that comprise the domain and multiplying the sum by the domain factor (see below).
The full scale score is obtained by adding the six domain scores. It should be noted that within the individual domains, a domain score of zero indicates that no sexual activity was reported during the past month.

Domain	Questions	Score Range	Factor	Minimum score	Maximum score
Desire	1, 2	1–5	0.6	1.2	6.0
Arousal	3, 4, 5, 6	0–5	0.3	0	6.0
Lubrication	7, 8, 9, 10	0–5	0.3	0	6.0
Orgasm	11, 12, 13	0–5	0.4	0	6.0
Satisfaction	14, 15, 16	0 (or 1)–5	0.4	0	6.0
Pain	17, 18, 19	0–5	0.4	0	6.0
		Full Scale Score Range		2.0	36.0

Appendix 7

Supportive Care Screening Tool



Please Affix Patient Label Here

Supportive Needs Screening Tool

Patient Details & Referral Form

SNST – REFERRAL FORM

MR/9F

Clinical Stream/Department

- O Breast
- O Gastrointestinal
- O Gynaecology
- O Haematology
- O Head & Neck
- O Lung
- O Neuro-oncology
- O Sarcoma
- O Skin & Melanoma
- O Urology

Date screening tool completed ___ / ___ / ___

Date discussion completed ___ / ___ / ___

Patient type

- O New patient
- O New recurrence
- O Repeat screening

Extent of disease

- O Diagnosis yet to be confirmed
- O Localised disease
- O Locally advanced disease
- O Metastatic disease
- O Definitive cancer diagnosis stage unknown
- O Systemic treatment with curative intent (Haem)
- O Systemic treatment with palliative intent (Haem)
- O Localised treatment with curative intent (Haem)
- O Localised treatment with palliative intent (Haem)

Patient geography

- O Rural
- O Metropolitan

Information provision

- O Written information provided to answer patient questions

Malnutrition Screening

Has the patient lost weight recently without trying?

- O Yes (0)
- O No (0)
- O Unsure (2)

If Yes, how much weight has the patient lost?

- O 0.5 - 5kg (1)
- O 5 - 10kg (2)
- O 10 - 15kg (3)
- O >15kg (4)
- O Unsure (2)

Has the patient been eating poorly because of decreased appetite?

- O Yes (1)
- O No (0)

TOTAL MALNUTRITION SCORE = 0 O 1 O 2 O 3 O 4 O 5 O

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Please Affix Patient Label Here

For Gynae-Oncology Service Only			
Are you currently sexually active?	O Yes	O No	O I would like to be
Do you have a partner?	O Yes	O No	
Do you have a sexual partner?	O Yes (m)	O Yes (f)	O No
Have you gone through menopause?	O Yes	O No	O Unsure
Are you currently using hormone therapy?	O Yes	O No	O Unsure
Has the effect of your treatment on your fertility been discussed with you?	O Yes	O No	O Unsure
Do you have any bleeding or discharge from the vagina?	O Yes	O No	O Unsure
Has anyone ever made you feel uncomfortable about your body?	O Yes	O No	O Unsure
	(O Possible history of sexual abuse)		

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Please Affix Patient Label Here

Supportive Needs Screening Tool

Patient Details & Referral Form

Referral recommended to patient	Referral accepted by patient	Reason for patient referral	Referral date
○ Clinical Psychology	○ Yes ○ No (please specify)	○ Lowered mood/tearfulness or social withdrawal ○ Irritability/anger ○ Worry/panic/distress ○ Cognitive concerns (eg memory difficulties or competence) ○ Other	__/__/__
○ Psychiatry	○ Yes ○ No (please specify)	○ Lowered mood/tearfulness or social withdrawal ○ Irritability/anger ○ Worry/panic/distress ○ Cognitive concerns (eg memory difficulties or competence) ○ Other	__/__/__
○ Community Service (please specify)	○ Yes ○ No (please specify)		__/__/__
○ Dentist	○ Yes ○ No (please specify)		__/__/__
○ Dietitian	○ Yes ○ No (please specify)	○ MST Score >= 2 ○ Other	__/__/__
○ Familial Cancer Centre	○ Yes ○ No (please specify)	○ CRC <50 yrs or CRC any age PLUS FH CRC/Gynae Cancer ○ Br Cancer <40 yrs or any age PLUS FH OvCa/multiple BrCa ○ Br Cancer or Ov Cancer PLUS 'at-risk' ancestry ○ Clustering of other cancers ○ Other	__/__/__
○ Nursing	○ Yes ○ No (please specify)	○ RT Link Nurse ○ Peter Mac @ Home ○ Stomal therapist	__/__/__
○ Occupational Therapy	○ Yes ○ No (please specify)	○ ADL assessment ○ Home management assessment ○ Fatigue management ○ Relaxation/stress management ○ Comfort/pressure care management ○ Other	__/__/__
○ onTrac@ PeterMac	○ Yes ○ No (please specify)	○ Patient aged between 15-25 ○ Other	__/__/__

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SNST – REFERRAL FORM

MR/9F

Please Affix Patient Label Here

Referral recommended to patient	Referral accepted by patient	Reason for patient referral	Referral date
O Pain & Palliative Care	O Yes O No (please specify)	O Complex symtom management O Palliative goal of cancer treatment - coordination of palliative modalities for patients approaching the end of life O Advanced cancer where death within 12 months would not be unexpected O Psychosocial needs of patient and carer in the context of the above mentioned point O Identified bereavement risks	__/__/__
O Pastoral Care	O Yes O No (please specify)	O Meditation O Support in relation to spiritual health and well-being O Other	__/__/__
O Physiotherapy	O Yes O No (please specify)	O Mobility assessment O Falls risk/balance problems O Shortness of breath O Fatigue O Strengthening/exercising O Lymphoedema O Other	__/__/__
O PISC	O Yes O No (please specify)	O Treatment/disease information O Information on support services O CAM information O Internet information O Information in other languages O Other	__/__/__
O Smoking Cessation Support	O Yes O No (please specify)	O Currently smoking O Considering quitting O Quit within the past six months O Other	__/__/__
O Social Work	O Yes O No (please specify)	O Full psychosocial assessment O Counselling O Adjustment support O Financial or practical issues O Home supports O Interpreter service O Music Therapy O Other	__/__/__
O Speech Therapy	O Yes O No (please specify)	O Difficulty swallowing O Difficulty speaking O Other	__/__/__
O Other (please specify)	O Yes O No (please specify)		__/__/__

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Appendix 8

Patient Education

Standard Education about Pelvic Radiotherapy to the Lower Gastrointestinal Tract

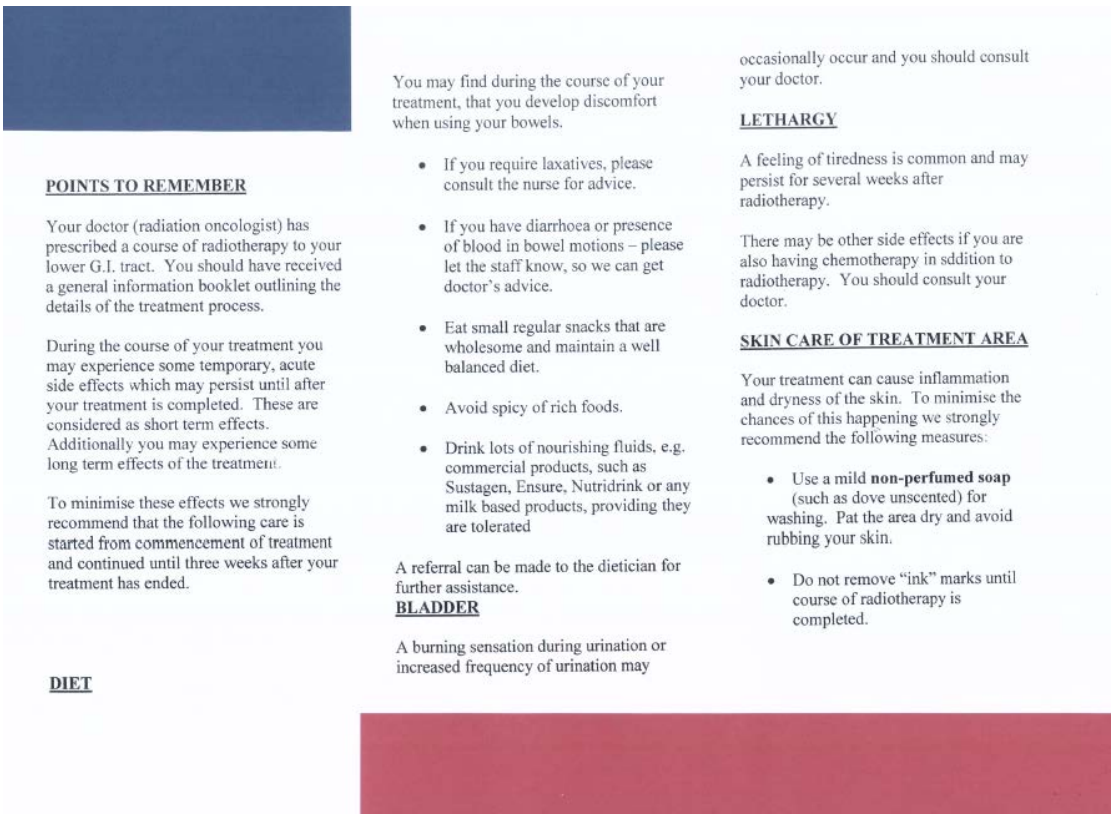
- Avoid perfume, spray on deodorants and talcum powder in the treatment area.
- Wear loose fitting clothing/nightwear.
- Use the sorbolene cream supplied by your nurse. Apply it to your treatment area twice daily. Always check with your doctor or nurse before using any other lotions, creams or ointment to your skin in the treatment area.
- Skin redness and discolouration may occur (tanning).
- Let your nurse know if you develop a severe irritation (itchiness/soreness) or redness in your redness in your treatment area.
- Maintain your skin care precautions for 3-4 weeks after treatment has completed

Peter Mac

RADIOTHERAPY TO LOWER G.I. TRACT

www.petermac.org
www.health.vic.gov.au/hsc/

Peter MacCallum Cancer Centre
St Andrews Place, East Melbourne Vic 3002
Postal Address:
Locked Bag 1, A'Beckett Street Melbourne Vic 8006
Telephone 03 9656 1111 Facsimile 03 9656 1400
ABN 42 100 504 883



POINTS TO REMEMBER

Your doctor (radiation oncologist) has prescribed a course of radiotherapy to your lower G.I. tract. You should have received a general information booklet outlining the details of the treatment process.

During the course of your treatment you may experience some temporary, acute side effects which may persist until after your treatment is completed. These are considered as short term effects. Additionally you may experience some long term effects of the treatment.

To minimise these effects we strongly recommend that the following care is started from commencement of treatment and continued until three weeks after your treatment has ended.

DIET

You may find during the course of your treatment, that you develop discomfort when using your bowels.

- If you require laxatives, please consult the nurse for advice.
- If you have diarrhoea or presence of blood in bowel motions – please let the staff know, so we can get doctor's advice.
- Eat small regular snacks that are wholesome and maintain a well balanced diet.
- Avoid spicy of rich foods.
- Drink lots of nourishing fluids, e.g. commercial products, such as Sustagen, Ensure, Nutridrink or any milk based products, providing they are tolerated

A referral can be made to the dietician for further assistance.

BLADDER

A burning sensation during urination or increased frequency of urination may occasionally occur and you should consult your doctor.

LETHARGY

A feeling of tiredness is common and may persist for several weeks after radiotherapy.

There may be other side effects if you are also having chemotherapy in sddition to radiotherapy. You should consult your doctor.

SKIN CARE OF TREATMENT AREA

Your treatment can cause inflammation and dryness of the skin. To minimise the chances of this happening we strongly recommend the following measures:

- Use a mild **non-perfumed soap** (such as dove unscented) for washing. Pat the area dry and avoid rubbing your skin.
- Do not remove "ink" marks until course of radiotherapy is completed.

Standard Education about Pelvic Radiotherapy and the Female Patient

Radiotherapy treatment to the pelvis for gastrointestinal, gynaecological and urological cancers will affect normal organs such as bowel, urethra and vagina.

Bowel linings will be inflamed. As a consequence, you will experience diarrhoea which can be controlled effectively with anti-diarrhoea medication (Lomotil or Gastrostop).

The urethra will be inflamed and you will experience dysuria (burning sensation when you pass urine accompanied by lower abdominal pain). This can be relieved by Ural medication with or without Cranberry juice. If symptoms persist, you will be tested for urinary infection and be treated appropriately.

The vaginal lining will be inflamed. It is an organ not frequently used and the potential space between the linings needs to be maintained to ensure it does not scar up or become fibrosed due to effects of radiotherapy. It needs to be kept patent for future gynaecological examinations and sexual function. Sexually active women often choose to abstain from sexual activity during their treatment although there is no medical reason for it. Women can continue to be sexually active throughout their treatment without any ill effects.

Vaginal Dilator Education and Counselling Material

What is vaginal stenosis?

Vaginal stenosis (or stricture) is defined as shortening and narrowing of the vagina due to inflammation of vaginal linings from pelvic radiotherapy. It can occur as early as four weeks or up to 3 months after completion of chemoradiation and the process can continue up to 3-5 years.

Vaginal stenosis happens as a result of inflammation, loss of normal cells in the vagina and ulceration of the linings. While it is healing, the inflamed vaginal wall can stick together. This causes a shortened, narrowed vagina. Vaginal elasticity is compromised. This can make pelvic examination and sexual intercourse difficult and painful. A thin and dry inner vaginal lining can easily crack causing some spotting of blood. Please note, this bleeding is not related to cancer.

Although vaginal stenosis cannot be completely prevented in all patients, there are steps that can be taken to reduce the chances of developing it.

A normal healthy vaginal lining requires lubrication. Applying a small amount of lubrication to the inner vaginal lining with the help of a vaginal cylinder will help reduce the risk of vaginal stenosis. The use of the vaginal cylinder is necessary for the delivery of lubricant to the entire vaginal lining.

What is the vaginal cylinder?

Vaginal dilators are smooth rigid cylinder-shaped pieces of plastic made of Delrin® acetal homopolymer. Delrin® is a non-allergenic crystalline plastic. They are manufactured at the Department of Radiation Engineering, Peter MacCallum Cancer Centre and is provided to you at no cost. Four standard sizes are available.

Your doctor will perform a vaginal examination before you commence chemoradiation and recommend an appropriate size for you. You may continue to be sexually active throughout their treatment without any ill effects.

If you have chosen to participate in the VERITAS study, please document the frequency of sexual intercourse per week.

In general, there are no anticipated serious adverse events associated with dilator use. You may experience minor discomfort.

When do I use the vaginal cylinder?

Standard recommendation for vaginal dilator use: initiate vaginal dilator insertion within 6 weeks of completing chemoradiation, insert 3 times per week for 5 minutes duration, as tolerated. You will need to apply a small amount of either lubricant or oestrogen cream onto the cylinder and gently insert it into the vagina (further instructions are included later in this leaflet).

If you choose to participate in the VERITAS Study, you will be asked to make note on the frequency and duration of use. Vaginal examinations will be performed to assess for side effects, and you will be asked to complete quality of life questionnaires.

What else can I do?

Pelvic floor muscles help control the bladder and bowel. It is important to keep theses muscles strong by doing some simple pelvic floor exercises. The also help with sexual function.
Strong pelvic floor muscles:
Prevent leakage from the bladder and bowel by keeping the urethra and anus tightly closed.
Support the pelvic organs when downward pressure is applied during sneezing, coughing and laughing.

Your doctor or nurse can provide further information about pelvic floor exercises if you are unsure about what to do.

Instructions

Pelvic floor muscle exercises
Pelvic floor muscles exercises should be undertaken three times a day (twice a day with your cylinder and once without).
Squeeze your pelvic floor muscles around the cylinder; hold as long and tight as you can, then relax. Repeat this 10 times. Try to build your hold up to 8-10 seconds.
Squeeze and lift your pelvic floor muscles. Do this as strongly and quickly as possible. Rest for a few seconds in between.

Vaginal Dilator Use
Using the vaginal cylinder and doing pelvic floor exercises
Wash your hands with soap and water before and after using the vaginal cylinder.
Apply the lubricant sparingly to the rounded end of the cylinder and the sides.
Find a position that is comfortable lying or standing.
Part the labia (lips of the vagina)
Push the rounded end of the cylinder gently into the vagina as far as it will go, this should not be painful.
Hold onto the vaginal cylinder so that it does not slide out.
Carry out pelvic floor muscle exercises as note under ’Pelvic floor muscle exercises’.
After you have used the vaginal cylinder wash it with soapy water, then rinse well. Dry with a lint free cloth and store it in a clean container or zip lock bag.

When do I start using the cylinder?
Within 6 weeks after radiotherapy treatment finishes.

How often do I use the cylinder?
Once a day, three times per week

How long should I leave the cylinder in my vagina?
Five minutes. Continue to use the vaginal cylinder as long as possible.

Lubricant

Water based lubricants can be bought from a pharmacy or supermarket. Oestrogen Cream can be used as an alternative.

After treatment follow-up

An appointment will be made for you to see the radiation oncologist at 4 weeks; and 3, 6, 9, 12, 18, 24 and 36 months after chemoradiation to monitor you progress and recovery. Your doctor or nurse will ask about any difficulties or concerns you might have with the use of vaginal dilators.

If you experience any problems using the vaginal cylinder or if you have any questions or concerns before this appointment please contact your doctor or your nurse.

Consult your doctor or nurse if you have:
A problem inserting the vaginal cylinder
Pain in the pelvic area
Persistent vaginal bleeding
Vaginal discharge
Pain with passing urine and increased frequency
Having trouble with pelvic floor muscles.

Contact Details

Call Peter MacCallum Cancer Centre Switchboard on 03 9656 1111 and ask for

Nurse:
Extension:

Doctor:
Pager:

Other:
Contact: