



A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: THE OUTBACK TRIAL (ANZGOG 0902)

Version 5.0, dated 09 May 2016

Principal Investigator:	Associate Professor Linda Mileschkin Peter MacCallum Cancer Centre St Andrews Place East Melbourne VIC 3002, Australia
Lead Radiation Oncologist:	Associate Professor Kailash Narayan Peter MacCallum Cancer Centre (as above)
Lead in Quality of Life:	Professor Madeleine King Quality of Life Office Psycho-oncology Co-operative Research Group (PoCoG) School of Psychology, Brennan MacCallum Building University of Sydney NSW 2006, Australia
Study Statistician:	Professor Val GebSKI NHMRC Clinical Trials Centre Locked Bag 77 Camperdown NSW 1450, Australia
Lead Collaborative Group:	ANZGOG: This is an independent multi-centre investigator-initiated study conducted under the auspices of ANZGOG.
Coordinating Centre:	NHMRC Clinical Trials Centre Lifehouse Building Level 6, 119 – 143 Missenden Road Camperdown NSW 2050, Australia Telephone: +61-2-9562-5000 Fax: +61-2-9562-5094
Participating Collaborative Group:	NRG Oncology (GOG & RTOG legacy groups)

The OUTBACK Trial

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1 PROTOCOL AUTHORISATION PAGE

CONFIDENTIAL

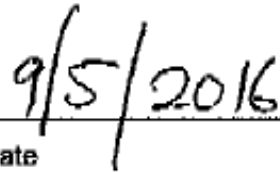
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A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone:
THE OUTBACK TRIAL



A/Prof Linda Mileshkin (protocol author)



Date



Prof Val Gebski (statistician)



Date

Note: Original and signed document held at the NHMRC Clinical Trials Centre

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2 ABBREVIATIONS

AP	Anterior-Posterior
ANZGOG	Australia New Zealand Gynaecological Oncology Group
AE	Adverse Event
ANC	Absolute Neutrophil Count
ALT	Amino Alanine Transferase
AST	Aspartate Amino Transferase
AUC	Area Under the Curve
CBC	Complete Blood Count
(e)CRF	(electronic) Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
CXR	Chest X-ray
CT	Computerised Tomography
DRR	Digital Reconstructed Radiograph
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
FIGO	International Federation of Gynecology and Obstetrics
GCIG	Gynecologic Cancer InterGroup
G-CSF	Granulocyte-Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GOG	Gynecological Oncology Group
Gy	Gray
HR	Hazard Ratio
HREC	Human Research Ethics Committee
IDSMC	Independent Data Safety Monitoring Committee
IMRT	Intensity-Modulated Radiation Therapy
IV	Intravenous
K	Potassium
L	Litre
ML	Millilitre
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
Mg	Magnesium
Na	Sodium
NCIC CTG	National Canadian Institute of Cancer Clinical Trials Group
NHMRC CTC	National Health & Medical Research Council Clinical Trials Centre
NS	Normal Saline
OS	Overall Survival
PA	Posterior-Anterior
PET	Positron Emission Tomography
PFS	Progression Free Survival
RT	Radiation Therapy
QA	Quality Assurance
QOL	Quality of Life
SAE	Serious Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMC	Trial Management Committee
ULN	Upper Limit of Normal

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3 SYNOPSIS

Title	A phase III trial of adjuvant chemotherapy following chemo-radiation as primary treatment for locally advanced cervical cancer compared to chemo-radiation alone: The OUTBACK Trial
Study Design	An international, prospective, multi-centre, randomised, phase III GCIG trial led by ANZGOG, in collaboration with the GOG, RTOG and India,
Patient population	Patients with stage IB1 & positive nodes, IB2, IIA, IIB, IIIB or IVA cervical cancer suitable for primary treatment with chemo-radiation with curative intent.
Intervention	<p>Radiotherapy regimen: All patients (Arm A and B) will receive 45 – 50.4 Gy external beam radiation therapy (EBRT) delivered in fractions of 1.8 Gy to the pelvis, followed by brachytherapy.</p> <p>Chemotherapy regimen: Cisplatin will be given during the radiation at a dose of 40mg/m² weekly for 5 doses to all patients (Arm A and B). Within 4 weeks of completion of all radiation treatment, and following recovery from toxicities, patients in Arm B will be treated with an additional 4 cycles of 3 weekly adjuvant chemotherapy using carboplatin AUC 5 and paclitaxel 155 mg/m².</p>
Primary Objective:	To determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemo-radiation improves overall survival.
Secondary objectives	To determine: progression-free survival rates, acute and long-term toxicities, patterns of disease recurrence, the association between radiation protocol compliance and outcomes and patient quality of life, including psycho-sexual health.
# patients	900
Planned duration	3 – 4 years recruitment and 3-5 years follow-up
Statistics	A total sample size of 900 (450 per arm) will have 80% power with 95% confidence of detecting a reduction in the hazard of death of at least 32% (hazard ratio 0.68) from the control regimen (approximate 8% improvement in overall survival at 5 years from 72% to 80%)

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4 BACKGROUND INFORMATION

In the majority of developing countries, cervical cancer remains the number-one cause of cancer-related deaths among women, with nearly 500,000 women diagnosed annually world-wide¹. Cervical cancer incidence has decreased in developed countries since the widespread introduction of cervical screening². For example, there were 734 new cases reported in Australia in 2005, which represents a 33% decline compared to 1991, although incidence has not declined subsequently³. Cervical cancer remains one of the leading causes of cancer-related morbidity and mortality world-wide, particularly in countries without screening programs, and in disadvantaged communities within developed countries with screening programs^{1,4,5}. For example, Aboriginal and Torres Strait Islander women have double the incidence and 5 times the mortality risk than other Australians^{3,6,7}. Human papilloma virus (HPV), particularly types 16 and 18, is significantly associated with subsequent development of cervical cancer, with an increased risk also seen amongst smokers¹.

Many patients with cervical cancer present with early-stage disease which is highly curable with surgical approaches or the use of chemo-radiation. However, a significant percentage of patients, particularly those who have not participated in screening programs, present with more advanced local disease and have much lower cure rates⁸⁻¹⁰. For example, in Australia, only 62% of eligible women had biennial participation in the National Screening Program during 2002-2006³. The recent introduction of the cervical cancer vaccine for children and young adults will reduce cervical cancer rates for the future generations but not the current one. Realising the benefit of the vaccine is predicted to take some time given that the incidence of cervical cancer continues to rise with age, and that ongoing screening will be required in addition to the vaccine program, which needs to be initiated prior to the age of commencement of sexual activity to be effective¹¹.

Standard therapy

The use of chemotherapy concurrent with radiation for cervical cancer has been proven to improve survival and has become established as standard care. A recent meta-analysis found that the addition of concurrent chemotherapy to radiation increased the 5 year overall survival rate by 6% (HR 0.81: 60 vs 66%)¹². However, in this analysis the 5 year disease-free survival rate was only 58% in the chemoradiation group, which although superior to the 50% in those patients treated with radiation alone, still leaves much room for improvement as the majority of patients who relapse are incurable¹³.

The main prognostic factor for outcome has traditionally been the FIGO staging system which is principally based on clinical examination alone for those patients deemed unsuitable for surgery. However, our centre and others have highlighted the significant prognostic role of both nodal and uterine corpus involvement as detected by imaging, with MRI and PET now accepted modalities for non-invasively determining these features¹⁴⁻¹⁶. Nodal involvement has been documented to predict disease relapse in multiple studies, however, it is not as yet considered by the current staging system^{14,17-20}. Uterine corpus invasion tends to be associated with tumours that grow endophytically

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and has also been shown to predict worse outcomes, in part because it appears to predict nodal metastasis²¹⁻²⁶.

For example, prospectively collected audit data from 436 patients treated at the Peter MacCallum Cancer Centre with primary chemo-radiation for locally advanced cervical cancer between December 1995 and December 2006 has demonstrated that patients with uterine involvement on MRI or node positive disease on PET scan have inferior survival outcomes. This group of patients reflects the current spectrum of patients being referred for chemo-radiation for cervical cancer, who often have never participated in the screening program^{8,9}. The median age was 63 years with 43% having stage II disease and 21% stage III or IV respectively. At a median follow-up of 5 years, the estimated 5 year failure-free rate for the whole group was 55%, with a median overall survival rate of 60%.

Overall 144 patients (33%) developed recurrent disease with only a small number recurring at the primary site alone, and three quarters relapsing in multiple sites. In those with PET positive nodal disease (n=132), 50% of patients developed recurrent disease versus 22% in the PET negative, with a 5 year overall survival of 48% in the PET positive and 70% in the PET negative group. In those with evidence of corpus uterine involvement on MRI (n=226), 46% recurred as compared to 17% without corpus involvement, with similar differences in 5 year overall survival (54 vs 71%), and corpus uterine involvement appearing to be a surrogate for the development of node positive disease. In both groups, a significant percentage of the recurrences involved distant metastases^{23,27,28}. Consequently in this trial we plan to stratify for the presence or absence of nodal disease, in addition to traditional factors such as FIGO stage, and will also perform a pre-planned subset analysis of the effect of adjuvant chemotherapy in these high-risk sub-groups. We also plan to try and validate within this prospective trial previous reports that a follow-up PET scan after completion of chemo-radiation can predict patient outcome²⁹.

The potential benefit from adjuvant chemotherapy

It is possible that the addition of further cycles of adjuvant chemotherapy following completion of chemo-radiation will decrease distant metastases and improve survival. Previous small retrospective studies using older style chemotherapy agents, such as anthracyclines, suggested no benefit and increased toxicity with the addition of adjuvant chemotherapy following chemo-radiation. However, the GOG109 study randomised patients with high-risk cervical cancer, initially treated with radical hysterectomy and pelvic lymphadenectomy, who were found to have positive pelvic nodes and/or positive margins and/or microscopic parametrial involvement to adjuvant radiation alone or adjuvant chemo-radiation. The chemotherapy consisted of 4 cycles of cisplatin and 5FU given as 2 cycles concurrent with radiation and 2 cycles post radiation. Progression-free and overall survival rates were significantly improved for patients who received the chemotherapy. Although only 60% completed all planned chemotherapy, higher numbers of chemotherapy courses received were favourably associated with improved progression-free and overall survival rates³⁰. This trial was one of 2 trials which gave additional chemotherapy after chemo-radiation and was considered in a

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subset analysis within the meta-analysis. In this group an absolute benefit of 19% in 5 year survival (from 60 to 79%) was seen^{30,31}.

More recent data presented at ASCO 2009 by Duenas-Gonzalez et al. showed a benefit of adding concurrent gemcitabine to the standard regimen of weekly cisplatin during radiation, followed by 2 further cycles of cisplatin-gemcitabine. This multi-centre randomised phase III trial performed in South America showed a statistically significant 9% improvement in the primary outcome of progression-free survival at 3 years from 65% to 74%, as well as in improvement in overall survival³². However, toxicity was significantly increased. Questions about the study have included uncertainty about the percentage of patients treated with radiation using Cobalt⁶⁰ rather than a linear accelerator, and surprise about the very high rates of radiotherapy delivery reported, particularly given that prior investigators using similar doses of cisplatin plus gemcitabine concurrent with radiotherapy in phase 1 studies have been unable to safely deliver the regimen. It also remains unclear how much the additional chemotherapy during radiation is actually improving outcomes as opposed to increasing toxicity. Hence a confirmatory trial to explore the benefit of adjuvant chemotherapy in cervical cancer is warranted. Because distant relapse is the main cause of patient death, this study will use standard cisplatin-based chemo-radiation but then test the addition of 4 cycles of adjuvant chemotherapy.

Choice of adjuvant chemotherapy

The combination of carboplatin and paclitaxel chemotherapy has been chosen for this study as it is active in metastatic cervical cancer and delivery has been shown to be feasible following pelvic chemo-radiation. In addition, cisplatin and paclitaxel have been demonstrated to have similar or better outcomes to cisplatin with topotecan, vinorelbine or gemcitabine for the treatment of metastatic disease in the recently published GOG 204 protocol. This combination has been recommended as an appropriate regimen to take forward as a standard control arm for future trials³³. In this study the lowest response rate was seen in those patients treated with cisplatin and gemcitabine, hence this regimen has not been chosen for use in this study despite the results from the Duenas-Gonzalez study. Quality of life data was also assessed in this study. The investigators found that no doublet was clinically or statistically different from cisplatin and paclitaxel in quality of life or pain.

Because of the concern about toxicity, especially neurotoxicity, with cisplatin, there has been interest in using carboplatin as a less toxic regimen. A trial published in 2005 looked at the combination of carboplatin and paclitaxel in advanced and recurrent cervical carcinomas and found a 20% partial response rate and a 20% complete response rate. The investigators concluded that carboplatin-paclitaxel was an active combination in advanced and recurrent cervical cancer³⁴.

Recently, a multi-institutional retrospective study reported on experience with paclitaxel and carboplatin versus paclitaxel and cisplatin in advanced-stage or recurrent cervical cancer. Moore et al found objective responses of 53% in the carboplatin group compared with 29% in the cisplatin group, with significantly less toxicity³⁵. Internationally, there has been a trend towards using

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carboplatin in cervical cancer, especially in patients previously treated with radio-sensitizing cisplatin³⁶⁻³⁸. Therefore, there is mounting evidence that the combination of paclitaxel and carboplatin is an effective and less toxic regimen in cervical cancer. The added benefit of ease of administration as a one day outpatient treatment makes this regimen an ideal choice to study in this population.

Preliminary data from the ongoing protocol GOG 209, treating advanced or recurrent endometrial cancer with paclitaxel, doxorubicin and cisplatin or paclitaxel and carboplatin, showed increased hematologic toxicities when patients were previously irradiated. This finding led to a protocol dose reduction for paclitaxel and carboplatin for women who have previously undergone pelvic irradiation. Similar findings in terms of haematological toxicity and also neurological toxicity have been seen in recently published retrospective data³⁶⁻³⁸. Consequently, we have modified our starting doses in the treatment arm of paclitaxel and carboplatin to reflect these data.

Assessment of patient quality of life including psycho-sexual health

An important component of this study will be to assess patient self-reported quality of life following chemoradiation +/- adjuvant chemotherapy for cervical cancer within the setting of a prospective trial. It is well recognised from surveys of cervical cancer survivors that some women will have reduced quality of life, related to chronic toxicities including bowel, urinary and sexual problems after treatment with radiotherapy³⁹⁻⁴¹. In some but not all reports, toxicity appears more pronounced in older patients^{42,43}. However, there has been a lack of patient reported outcomes within chemo-radiation studies to date, and this trial represents a unique opportunity to address this issue^{44,45}. Collecting such data as part of this trial will help to define the scope of the problem and potentially identify which subsets of women are most at risk of having significant chronic toxicities including psycho-sexual problems after treatment.

Taken together, these data reinforce the need for an adequately powered trial testing the role of adjuvant chemotherapy treatment in cervical cancer. A phase III randomised trial, comparing chemo-radiation and adjuvant chemotherapy with chemo-radiation alone in patients with cervical cancer will establish the role of adjuvant chemotherapy in this patient population.

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5 AIMS AND OBJECTIVES

The **aim of this study** is to test the potential benefit of the addition of adjuvant chemotherapy following completion of primary chemoradiation for patients with locally advanced cervical cancer.

The **primary objective** will be to determine if the addition of adjuvant chemotherapy to standard cisplatin-based chemoradiation improves overall survival.

Secondary objectives will be to determine:

- Progression-free survival rates
- Acute and long-term toxicities
- Patterns of disease recurrence
- The association between radiation protocol compliance and outcomes
- Patient quality of life, including psycho-sexual health

Tertiary objectives will be to determine:

- The association between the results of a follow-up PET scan performed 4 – 6 months post completion of chemo-radiation and outcomes for all patients in the trial
- Biological predictors of patients outcomes based on translational laboratory studies of blood and tissue specimens

6 TRIAL DESIGN

The study design is a multi-centre randomised phase III trial.

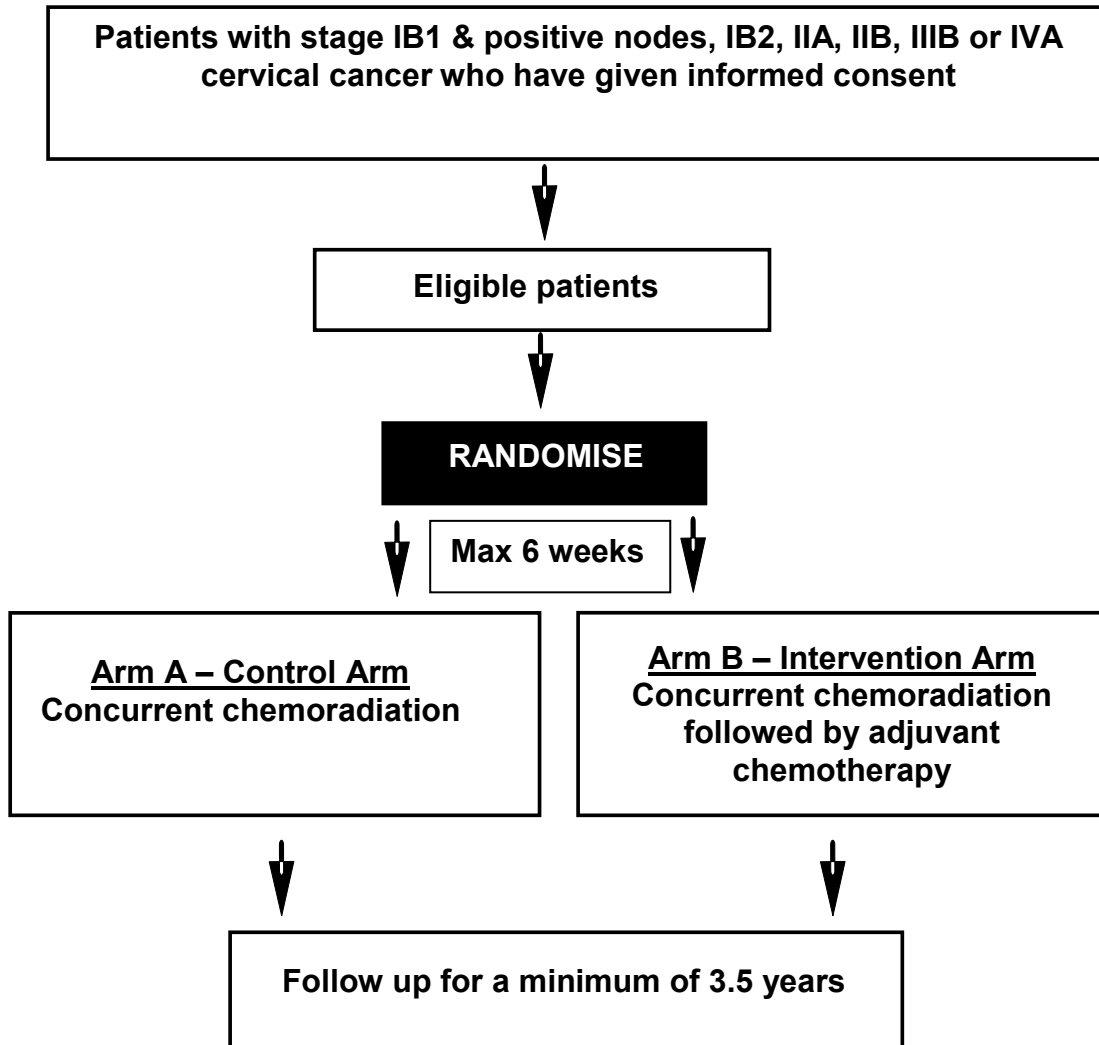
Arm A: Standard chemoradiation

Arm B: Standard chemoradiation followed by 4 cycles of carboplatin and paclitaxel

Patients in both arms will be treated with standard external beam radiation treatment to the pelvis and brachytherapy. Cisplatin will be given during the radiation at a dose of 40mg/m² weekly for 5 doses. Within 4 weeks of completion of all radiation treatment, including the brachytherapy component, and following recovery from toxicities, patients in Arm B will be treated with 4 cycles of 3 weekly adjuvant chemotherapy using carboplatin AUC 5 and paclitaxel 155 mg/m².

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6.1 Study Schema



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6.2 Randomisation

Patients will be randomised to either: standard chemoradiation or standard chemoradiation plus adjuvant chemotherapy, using the method of minimisation. Randomisation will be performed by sites through a web-based system. Randomisation will be 1:1 to each treatment arm and patients will be stratified by the following factors:

Stratification factors

- Pelvic or common iliac nodal involvement: Yes or No or Unknown (Patients may be considered node-positive based on staging PET/CT scan results, or staging CT/MRI results if >15mm short axis diameter, or surgical nodal biopsy or resection leading to abandonment of planned hysterectomy. The method of determining whether the patient has node positive disease should be recorded)

Any node(s) within the pelvis below the common iliac bifurcation, such as obturator, internal or external iliac nodes are called pelvic nodes. Nodes above this bifurcation along the common iliac vessels up to the origin of common iliac vessels where the aorta bifurcates are called common iliac nodes. The aortic bifurcation occurs usually at the level of the fourth lumbar vertebrae (L4 Vertebra), just above the confluence of the left and right common iliac veins.

- Requirement for extended-field radiotherapy treatment (Yes or No)

If the pelvic field is at or below the intervertebral disc between L4-L5 it will be regarded as pelvic field. When the upper border of the treatment field is located above this plane, anywhere up to T12-L1, it will be regarded as EFRT.

- FIGO 2008 Stage IB / IIA or IIB or IIIB / IVA
- Age <60 or ≥60 years
- Hospital/site

6.3 Endpoints

The primary endpoint will be the overall survival rate at 5 years.

The secondary endpoints will be:

- The progression-free survival rate at 3 and 5 years
- The rate of acute and long-term toxicities
- The patterns of disease recurrence
- Radiation protocol compliance
- Patient self-reported quality of life including psychosexual health

A tertiary endpoint will be:

- The rate of complete and partial metabolic response on a PET scan performed 4 – 6 months after completion of chemo-radiation treatment

7 SUBJECT POPULATION

7.1 Inclusion criteria

Eligible patients will have locally advanced cervical cancer suitable for primary treatment with chemo-radiation with curative intent, in addition to:

- FIGO 2008 stage IB1 & node positive, IB2, IIA, IIB, IIIB or IVA disease.
- Age 18 years or older
- ECOG performance status 0 - 2
- Histological diagnosis of squamous cell carcinoma, adenocarcinoma or adenosquamous cell carcinoma of the cervix
- WBC $\geq 3.0 \times 10^9/L$ and ANC $\geq 1.5 \times 10^9/L$
- Platelets $\geq 100 \times 10^9/L$
- Bilirubin $\leq 1.5 \times ULN$
- AST or ALT $\leq 2.5 \times ULN$ (if both tests are done, both results need to be $\leq 2.5 \times ULN$)
- Adequate renal function: creatinine $\leq ULN$ (CTC Grade 0) or calculated creatinine clearance (Cockcroft-Gault Formula) $\geq 60ml/min$ or $\geq 50 ml/min$ by EDTA creatinine clearance
- Written informed consent

7.2 Exclusion criteria

- Any previous pelvic radiotherapy
- Para-aortic nodal involvement above the level of the common iliac nodes or L3/L4 (if biopsy proven, PET positive or $\geq 15mm$ short axis diameter on CT)
- FIGO 2008 stage IIIA disease
- Patients assessed at presentation as requiring interstitial brachytherapy treatment
- Patients with bilateral hydronephrosis unless at least one side has been stented and renal function fulfils the required inclusion criteria
- Previous chemotherapy for this tumour
- Evidence of distant metastases
- Prior diagnosis of Crohn's disease or ulcerative colitis
- Peripheral neuropathy \geq grade 2 (as per CTCAE v4)
- Patients who have undergone a previous hysterectomy or will have a hysterectomy as part of their initial cervix cancer therapy. This includes patients with a prior history of supracervical hysterectomy
- Patients with other invasive malignancies, with the exception of non-melanoma skin cancer and in situ melanoma, who had (or have) any evidence of the other cancer present within the last 5 years
- Patients who are pregnant or lactating
- Any contraindication to the use of cisplatin, carboplatin or paclitaxel chemotherapy

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- Serious illness or medical condition that precludes the safe administration of the trial treatment including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements
- Patients who are known to be HIV positive

7.3 *Withdrawal criteria*

Participation in this study is voluntary; patients will be able to withdraw at any time. A patient may withdraw, or be withdrawn, from study treatment for the following reasons:

- Intercurrent illness which prevents further follow up
- Withdrawal of consent for treatment by patient
- Any alterations in the patient's condition which justifies the discontinuation in the investigator's opinion

If a patient or investigator decides to stop the study treatment then the patient's health status will be reviewed via continued study visits or phone contact, or from their general practitioner or medical records to allow collection of outcomes data. Follow-up assessments including completion of the quality of life questionnaires should still be completed as per section 9 if the patient is willing. In the event that a patient withdraws from the study entirely, the effective date of the notification will be the date on which their withdrawal is received by the OUTBACK study team. No information about the patient will be collected from that point in time onwards but any information collected prior to that date can be used and forms part of this study.

7.4 *Patient transfers*

For patients moving from the area, every effort should be made for the patient to be followed up at another participating trial centre and for this trial centre to take over responsibility for the patient. A copy of the patient CRFs will need to be provided to the new site after appropriate patient consent. Until the new centre formally agrees (in writing) to take over responsibility, the patient remains the responsibility of the original centre.

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8 TREATMENT OF SUBJECTS

Study treatment must start within 6 weeks after randomisation.

8.1 Chemotherapy administration

Cisplatin, paclitaxel and carboplatin should be given in the doses and schedule detailed below, according to standard practice in the participating country. Suggested pre- and post-chemotherapy medication and hydration guidelines are detailed below. For detailed information on each drug, please refer to the relevant Summary of Product Characteristics in the package insert.

Dose calculation: The dose will be calculated using actual body weight. Dose capping of cisplatin and paclitaxel should not be done for obese patients as per the recent ASCO guidelines. The doses of all chemotherapy agents should be re-calculated if there is a weight change of >10% from baseline. Doses should not be increased following a dose reduction because of toxicity.

8.1.1 Concurrent phase (both treatment arms)

Agent	Dose/day	Route	Frequency
Cisplatin	40 mg/m ² in 1000 ml NaCl 0.9% or 2.5-3%*	IV in 1 hour with associated hydration	Weekly for 5 doses**

* According to local standard protocol. Cisplatin should only be given on a day that external-beam radiation is scheduled and must be given prior to radiation treatment on that day. Treatment should preferably be given on a Monday, Tuesday or Wednesday. Cisplatin should commence within the first 3 radiation treatments. Cisplatin should not be given on a day of brachytherapy treatment.

** For consistency between treatment arms, all patients should be planned to receive 5 doses regardless of the radiation fractionation schedule planned.

Published studies of prospective randomised trials to date have not compared whether there is a difference in outcome based on whether 5 or 6 cycles of weekly cisplatin are received during radiation. However, a retrospective review of data from the GOG120 and 165 studies found no difference in survival outcomes for patients treated with either 5 or 6 cycles of weekly cisplatin⁴⁶. There has been a further recent retrospective study published of 118 patients treated with cisplatin-based chemo-radiation for locally advanced cervical cancer in which no difference in survival was seen in patients treated with 5 or 6 cycles of weekly cisplatin, although inferior survival was seen in those treated with less than 5 cycles⁴⁷.

The MRC individual patient data meta-analysis reports that 'for the eight trials that used cisplatin-based chemo-radiotherapy, we found no evidence that the effect of chemo-radiotherapy differed according to the cycle length or the dose-intensity of cisplatin used'¹². It has been noted in several trials that only 50-70% of patients are able to complete a full 6 cycles of cisplatin without dose decreases or delays due to toxicity, primarily haematologic⁴⁶⁻⁴⁹.

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Suggested schedule for pre- and post-hydration: Pre-hydration: 1000 ml NaCl 0.9% in 2 hours followed by 400ml of 10% Mannitol over 30 minutes. Post-hydration: 1000 ml NaCl 0.9% in 2 hours, with adequate IV supplementation of Mg. Other schedules (if used in standard protocols) may be chosen at the participating centre's discretion.

8.1.1.1 Dose modifications of cisplatin

All toxicities will be graded according to the US National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v4.0 (CTCAE). It is recommended that anaemia > grade 1 (i.e. Hb <10 g/dL) during chemoradiation be corrected with blood transfusion as soon as possible. There will be no dose escalations in this study. Chemotherapy will not be administered during a radiation therapy delay. Radiotherapy will not be omitted or delayed for chemotherapy-related toxicities unless the investigator considers the patient too ill to be treated. If a cisplatin cycle is delayed due to a radiation therapy delay, then this can be made up if the patient is still receiving external beam radiation therapy in the 6th or 7th week of treatment.

Initial treatment modifications will consist of cycle delay and/or dose reduction as directed.

Treatment decision will be based on absolute neutrophil count (ANC) not total white blood cell count (WBC) on the day of treatment or no more than 72 hours prior. No cisplatin will be administered or resumed until ANC is $\geq 1.5 \times 10^9/L$ and/or platelet count is $\geq 75 \times 10^9/L$. Chemotherapy will be delayed week-by-week until these levels are exceeded. External radiation should continue while cisplatin is being withheld. **Patients who fail to recover from toxicities within 21 days will not receive further cisplatin.. Only one dose reduction is allowed for cisplatin. Patients in the experimental arm (Arm B) are allowed to continue with adjuvant chemotherapy if chemoradiation toxicities (with the exception of lymphocyte count) resolve to < grade 2.**

Drug	Starting dose level	Dose level -1
Cisplatin	40mg/m ²	30mg/m ²

DRUG-RELATED TOXICITY	PARAMETER	MODIFICATION
Febrile neutropenia/ANC	1 st occurrence febrile neutropenia (\geq grade 3) or ANC < $0.5 \times 10^9/L$ lasting > 7 days	Hold for 1 week. Repeat bloods. If ANC resolves to grade 1, resume at 1 dose level reduction. If ANC does not resolve to grade 1 discontinue cisplatin
Febrile neutropenia/ANC	2 nd occurrence	Discontinue cisplatin
ANC	Uncomplicated (no fever/infection) ANC < $0.5 \times 10^9/L$ lasting < 7 days	No dose reduction but not for re-treatment until ANC resolves to grade 1

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Platelets	1 st occurrence grade 4 thrombocytopenia or bleeding associated with grade 3 thrombocytopenia	Hold for 1 week. Repeat blood work. If platelets $>75 \times 10^9/L$, resume at 1 dose level reduction. If thrombocytopenia does not resolve to grade 1 discontinue cisplatin
Platelets	2 nd occurrence of above	Discontinue cisplatin
Platelets	Grade 3 – uncomplicated (absence of associated bleeding)	Hold until platelets $>75 \times 10^9/L$ Resume at current dose level (no dose modification)
Nausea/vomiting	Grade 3 or 4	Hold until resolved to grade 1 with supportive therapy. Resume at 1 dose level reduction
Nausea/vomiting	2 nd occurrence of above	Discontinue cisplatin
Serum creatinine/GFR	GFR < 50 ml/min (Cockcroft Gault), and/or Serum creatinine $> 1.5 \times$ ULN GFR < 40 ml/min (measured creatinine or EDTA clearance)	Hold for 1 week. Repeat blood work. Resume if GFR recovers to above these levels at the same dose. Discontinue cisplatin if not recovered after 1 week
Neurotoxicity – peripheral neuropathy	\geq Grade 2	Hold until neuropathy resolves to grade 1. Resume at 1 dose level reduction. Discontinue cisplatin if neuropathy does not resolve within 21 days
Tinnitus or hearing impaired	Grade 3 or 4	Discontinue cisplatin
Tinnitus or hearing impaired	Grade 2	Hold until recovery to grade 1, then resume at one dose level reduction. An audiogram should be performed to clarify if possible irreversible hearing loss
Fatigue	Any grade	No dose reduction

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Other cisplatin –related non-haematologic toxicity (except for non-clinically significant laboratory abnormalities such as lymphocyte count)	≥ Grade 3	Hold until toxicity resolved to grade 1, then resume at same dose. If toxicity does not resolve to grade 1 within 21 days discontinue cisplatin
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8.1.2 Adjuvant phase (Arm B only)

8.1.2.1 Carboplatin and paclitaxel dose

Agent	Dose/day	Route	Days
Paclitaxel	155 mg/m ²	IV in 3 hours	1, 22, 43, 64
Carboplatin	AUC 5 (calculated AUC)	IV in 1 hour	1, 22, 43, 64

Four cycles of adjuvant therapy with carboplatin and paclitaxel will be given, at 3 week intervals. Nano –particle albumin bound paclitaxel must not be used. Adjuvant chemotherapy should be started within 4 weeks of completion of all radiotherapy, meaning all external beam radiotherapy and brachytherapy, and preferably 3-4 weeks after the last administration of cisplatin. If adjuvant chemotherapy is not planned to commence for more than 6 weeks after completion of all radiotherapy, this should be discussed with the study chair. Before starting adjuvant chemotherapy, the toxicities of the concomitant chemoradiation should be resolved to less than grade 2 (except for lymphocyte count). Doses should be calculated based on the weight and laboratory results at the time of start of adjuvant chemotherapy. Dose capping of paclitaxel should not be used as per the ASCO Guideline for Chemotherapy Dosing in Obese adults.

Carboplatin dose is to be calculated according to the Calvert formula:

$$\text{Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25),$$

where AUC = Area under curve

GFR should be calculated according to Cockcroft-Gault Formula for females:

$$\text{GFR (ml/min)} = [1.05 \times (140 - \text{age}) \times \text{weight (kg)}] / \text{serum creatinine (umol/L)}$$

Actual weight should be used for estimation of GFR for patients with BMI of less than 25.

Adjusted weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**.

Adjusted weight calculation:

$$\text{Ideal weight (kg)} = (((\text{Height (cm)}/2.54) - 60) \times 2.3) + 45.5$$

$$\text{Adjusted weight (kg)} = ((\text{Actual weight} - \text{Ideal weight}) \times 0.40) + \text{Ideal weight}$$

A nuclear medicine GFR result may be performed if there is concern about the accuracy of a calculated GFR result, e.g. result > 100ml/min, serum creatinine very low, the patient is obese or

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very underweight, or the patient has pre-existing renal impairment or ureteric obstruction. AUC for carboplatin should be recalculated in case of increasing serum creatinine (increase of 10% and/or out of normal range) and/or weight change of >10% from the start of adjuvant chemotherapy.

The dose for paclitaxel should be recalculated in case of weight change of >10% from the start of adjuvant chemotherapy.

The GFR used in the Calvert formula should not exceed 125 ml/min. If the calculated or measured value is > 125 ml/min then it should be capped at 125 ml/min.

The maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

The maximum allowed dose of carboplatin is AUC 5 = 750 mg.

8.1.2.2 Dose modifications for carboplatin and paclitaxel

Adjustments for haematological toxicity

Pre-treatment neutrophil count should be $\geq 1.5 \times 10^9/L$ and platelet count $\geq 100 \times 10^9/L$ on the day of treatment or within 72 hours prior. If counts are below these levels, treatment should be delayed one week. If counts have recovered after one week, treatment should proceed at the starting doses. If counts have not recovered after one week, treatment should be delayed an additional week. If counts have recovered after the additional week's delay, doses should start at the reduced dose levels. If counts have not resolved after 2 weeks, no further chemotherapy should be given.

Drug	Starting dose level	Dose level -1
Carboplatin	AUC 5 (calculated AUC)	AUC 4
Paclitaxel	155 mg/m ²	135 mg/m ²

TOXICITY	PARAMETER	MODIFICATION
Febrile neutropenia/ANC	1 st occurrence febrile neutropenia (\geq grade 3) or ANC $< 0.5 \times 10^9/L$ lasting > 7 days	Hold for 1 week. Repeat blood work. If ANC resolves to grade 1 resume at 1 dose level reduction. If ANC does not resolve to grade 1 by 2 weeks discontinue carboplatin and paclitaxel
Febrile neutropaenia/ANC	2 nd occurrence of above	Discontinue carboplatin and paclitaxel

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Platelets	1 st occurrence grade 4 thrombocytopenia or bleeding associated with grade 3 thrombocytopenia	Hold for 1 week. Repeat blood work. If platelets >100 x 10 ⁹ /L resume at 1 dose level reduction. If thrombocytopenia does not resolve to grade 1 by 2 weeks discontinue carboplatin and paclitaxel
Platelets	2 nd occurrence of above	Discontinue carboplatin and paclitaxel

Adjustments for Non-Haematological toxicity

The following table should be used for dose reductions in the event of any grade 3 or 4 non-haematological toxicity excluding alopecia, nausea or constipation that lasts for more than 1 week. In the event of a grade 3 or 4 non-haematological toxicity apart from those specifically discussed below, doses should be reduced by one dose level and treatment given after recovery of the toxicity to be less than grade 2, if recovery has not occurred after a week delay. If the toxicity does not recover to be less than grade 2 after 2 weeks, then no further chemotherapy should be given. If a patient develops recurrent grade 3 or 4 non haematological toxicity at dose level -2, the patient should come off study treatment.

Drug	Starting dose level	Dose level -1	Dose level -2
Carboplatin	AUC 5	AUC 4	Additional 10% reduction in dose used for Dose level -1
Paclitaxel	155 mg/m ²	135 mg/m ²	110 mg/m ²

TOXICITY	PARAMETER	MODIFICATION
Peripheral neuropathy	≥ Grade 2	Reduce paclitaxel by 1 dose level and delay subsequent therapy for a maximum of 2 weeks until recovery to Grade 1. If the neuropathy does not recover to be less than Grade 2, the patient should continue with carboplatin alone

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Hepatic toxicity	≥ Grade 3 elevations in AST, ALT or bilirubin	Reduce paclitaxel by 1 dose level, but NOT carboplatin, and delay subsequent therapy for a maximum of 2 weeks until recovery to Grade 2. If the hepatic toxicity does not recover to be less than Grade 2 the patient should continue with carboplatin alone
Serum creatinine	≥ Grade 2	Hold for 1 week. Repeat blood work. Delay subsequent therapy for a maximum of 2 weeks until recovery to Grade 1, then resume at one dose level reduction. If the creatinine does not recover to be less than Grade 2, then no further chemotherapy should be given

The occurrence of a hypersensitivity reaction to paclitaxel is not considered a toxicity requiring dose adjustment and should be managed as per usual institutional practice. Patients may be retreated at full doses after management as per usual institutional practice. For example, following administration of medication to prevent hypersensitivity reactions, a slow initial infusion rate of paclitaxel should be utilized which is gradually increased to the standard infusion rate in the absence of a reaction. In case of severe hypersensitivity to paclitaxel, where rechallenge is not medically indicated **or** if repeated severe reaction at rechallenge, paclitaxel can be substituted by docetaxel 75 mg/m². In case of hypersensitivity to docetaxel as well or where docetaxel is not available, continue with carboplatin AUC 5. In case of severe hypersensitivity to carboplatin, where rechallenge is not medically indicated **or** if repeated severe reaction at rechallenge, carboplatin could be substituted by cisplatin 50 mg/m².

8.2 Concomitant Medications/Treatments

8.2.1 Concomitant chemoradiation:

Anti-emetic therapy before the start of cisplatin: aprepitant 125 mg, dexamethasone 8 mg, ondansetron 8 mg; or use a standard combination of a corticosteroid and a 5HT-antagonist (the use of aprepitant is at discretion of the participating centre).

After administration of chemotherapy, anti-emetic therapy is at discretion of the participating centre.

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8.2.2 Adjuvant chemotherapy:

Premedication before the start of carboplatin and paclitaxel: dexamethasone 20 mg i.v., phenergan 25 mg orally, ranitidine 50 mg i.v. and a 5HT-antagonist (the use of aprepitant is at discretion of the participating centre) or a similar schedule at the discretion of the participating centre.

After administration of chemotherapy, anti-emetic therapy is at the discretion of the participating centre.

Use of G-CSF is permitted for secondary prophylaxis after a neutropenic complication according to the American Society of Clinical Oncology guideline (2006 Update of ASCO Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline).

Further anti-cancer therapy should not be instituted following completion of study treatment unless progressive disease is documented.

8.3 Radiotherapy Treatment

This is a prospective multi-national trial investigating the addition of adjuvant chemotherapy following completion of primary chemo-radiation for patients with locally advanced cervical cancer. The incidence of cervix cancer has decreased in developed countries, but remains one of the leading causes of cancer-related morbidity and mortality in developing countries. Many of the trial participants are likely to be from developing countries. It is recognised that these countries have limited resources and infrastructure. Their participation is necessary not only for the successful completion of this study but to ensure that any treatment protocols that are developed through such studies are applicable in countries where cervix cancer is most prevalent. The protocols and quality assurance criteria for this trial have been designed to enable participation from both advanced and developing countries and centres.

Radiation therapy (RT) must be started within six weeks of randomisation; CT scan or MRI of the pelvis is recommended but not required for external RT field and block definition.

8.3.1 Standardized Radiotherapy

External beam radiotherapy followed by intracavitary brachytherapy.

External Irradiation

8.3.1.1 EBRT Radiation Equipment

Radiation beams must be of megavoltage energy with a source to surface distance (SSD) of 80 cm or greater. Use of linear accelerators and Cobalt 60 units are allowed.

8.3.1.2 EBRT Technique and Doses

All patients should be treated with whole pelvic radiotherapy. Those with common iliac nodal disease should be treated with extended field radiotherapy (EFRT).

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A four-field box technique with parallel opposed AP/PA and two opposing lateral fields is recommended. AP/PA only fields are allowed in thin women at the discretion of the treating physician. A thin woman is defined as one for whom the AP/PA midplane percent depth dose is 72% or more, or for isocentric treatments, the tissue-maximum ratio (TMR) is 0.82 or more.

Due to constraints on quality assurance capabilities highly conformal techniques such as IMRT and Rapid Arc are not permitted

Patients will receive 45 – 50.4 Gy external beam radiation therapy (EBRT) delivered in fractions of 1.8 Gy to the pelvis.

Patients with involved nodes where EBRT may be needed will receive 45 Gy in fractions of 1.8 Gy to extended field.

Treatments are to be delivered daily. At the end of EBRT, if intracavitary brachytherapy (BT) cannot be performed, shrinking field technique should be employed to bring gross tumour volume, with adequate margins, to a minimum of 65 Gy. An attempt should be made to exclude small bowel from the treatment field after 50.4 Gy. Interstitial brachytherapy is not permitted on this study.

8.3.1.3 EBRT Treatment aids/equipment

Patients may be treated with bladder distension. Bowel exclusion devices (e.g. belly boards) are allowed.

8.3.1.4 Parametrial or nodal boost

Parametrial or nodal boost is allowed at the discretion of the treating radiation oncologist. Nodal involvement is defined as any pelvic or common iliac nodes if they are either PET positive or their short axis diameter is > 15mm on CT and/or MRI or if nodes are found to be histologically positive on surgical sampling.

Doses to the parametrial/nodal boost should not exceed 10 Gy with a total dose to the sidewall not to exceed 65 Gy at midplane. Fractions of 1.8-2 Gy can be used. Point B may be used as the calculation point dose site if the boost is in the parametrial region.

For a parametrial boost the superior border should be reduced to include only the true pelvis. The upper border of the true pelvis field is defined as 1.0 cm above the inferior aspect of the sacroiliac joint.

If nodal involvement is documented, fields with up to 2.0 cm margin around the gross nodal disease as seen on the CT scan, MRI or PET is recommended. Nodal boost fields can be delivered via conformal fields.

8.3.1.5 Timing of the parametrial and/or nodal boosts

The nodal / parametrial boosts can occur after completion of EBRT and in between the brachytherapy insertions.

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8.3.1.6 EBRT Fractionation

Conventional fractionation will consist of one fraction per day, total five fractions per week. (Exceptions are six fractions per week for 1 -2 weeks to ensure overall treatment time stays within limits and to facilitate brachytherapy bookings.)

8.3.1.7 Therapy interruptions

Reasons for interruption to external beam radiation of greater than one week, (7 consecutive days), should be recorded.

8.3.1.8 EBRT imaging for localization and verification

Diagnostic CT scan or MRI is strongly recommended for pre-treatment planning.

All patients must undergo simulation using x-ray or CT for localization and verification of external beam treatment portals.

8.3.1.9 External radiation fields

The external beam target volume should encompass, with adequate margins, the gross tumour volume (GTV) which includes the primary cervical tumour and its gross extension and any grossly involved lymph nodes. Clinical target volume should include the GTV, parametria, uterus, upper half of the vagina, internal, external and distal common iliac nodes, and utero-sacral ligaments.

8.3.1.10 Four-field external beam technique

Whole Pelvis AP/PA fields:

Radiation portals should consist of a typical pelvic field, the upper border being L5 – S1 or L4-L5. The lateral borders should be marked 2 cm lateral to true pelvis and inferior borders at the lower margins of the obturator foramina or 3 cm below the known inferior extent of the gross disease (whichever is most caudal). Where possible, the femoral heads should be blocked.

Whole Pelvis Lateral fields:

The upper and lower borders of the lateral fields should be the same as in the AP/PA fields. The anterior border of the pelvic field should be 1 cm anterior to the superior edge of pubic symphysis and the posterior border should intersect the S2-S3 space or 3 cm posterior to the uterine outline or any gross disease whichever is greater. Custom shielding should be designed such that gross disease is encompassed with at least a 2 cm margin. The outer table of the sacrum may be blocked to protect the sacral plexus on lateral fields, and the small bowel should be blocked in the anterior-superior lateral fields.

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EFRT AP/PA fields

See whole pelvis description for pelvic limits.

These fields should encompass the highest involved node with a margin of 3 cm or one vertebral body cephalad, to a maximum upper level of L1/L2 vertebral space. Lateral margins above L4 vertebral body should be at least 6 cm wide or a minimum of 2 cm lateral to the lateral border of involved lymph node, whichever is greater. Special consideration should be taken to block the kidneys. The dose should be no higher than 1.8 Gy per fraction.

EFRT Lateral fields

See whole pelvis description for pelvic limits

The anterior border of chimney part of EFRT should be 3 cm anterior to the anterior surface of the vertebral body or 2 cm anterior to the anterior surface of any enlarged node. Posterior border of the chimney field should follow the spinal curve with a 5 -7 mm margin anterior to the spinal canal provided the involved nodes are adequately covered.

8.3.2 Intracavitary Brachytherapy

8.3.2.1 Brachytherapy (BT) Radiation Equipment

Intracavitary treatment will be delivered with standard applicators; tandem and ovoids or tandem and ring. A tandem and cylinder is allowed only for patients where tandem and ovoid application is not possible due to extent of disease or vaginal anatomy.

Interstitial brachytherapy should not be part of the original treatment plan for radiotherapy. Patients assessed as requiring interstitial brachytherapy at diagnosis are not eligible. However, if it is felt to be clinically imperative to change the plan after treatment start to deliver interstitial brachytherapy because of poor response of the tumour to external beam radiotherapy then this should be recorded.

The dose prescription and reporting in this situation will be the isodose line at the perimeter of the implanted volume, where dosimetric constraints similar to “point A” will apply.

8.3.2.2 BT Doses

Brachytherapy should deliver a dose to the primary tumour such that the primary tumour receives 80 – 86.4 Gy in total, from the combination of EBRT and BT. **See Tables 1 and 2 for examples.**

Table 1. LDR – Point A determined implant

Total EBRT (Gy) at 1.8 Gy/fx	Number of LDR Fractions	Dose per fraction (Gy)	Total LDR point A dose (Gy)	Total point A dose (Gy)
45	1	35-40	35-40	80-85
45	2	18-20	36-40	81-85
50.4	1	30-35	30-35	80.4-85.4
50.4	2	15-18	30-36	80.4-86.4

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Table 2. HDR- Point A determined implant or volume directed approach

Total EBRT (Gy) at 1.8 Gy/fx	# HDR fractions	HDR Point A dose/fraction (Gy)	Total HDR Point A dose (Gy)	Total Point A EQD2 –Gy ₁₀
45	3	8.4	25.2	82.9
45	4	6.8	27.2	82.3
45	5	5.8	29.0	82.4
50.4	3	7.5	22.5	82.4
50.4	4	6.1	24.4	82.3
50.4	5	5.2	26	82.5

Where EQD2 = Total Biological Equivalent Dose in 2 Gy Fractions

8.3.2.3 BT imaging for localization and verification

Orthogonal x-ray films, ultrasound, CT or MRI can be used to calculate dosimetry for brachytherapy insertions.

Ideally, soft tissue imaging (trans-abdominal ultrasound, CT or MRI) with applicator in-situ should be performed at each insertion to confirm the position of the tandem within the uterus.

8.3.2.4 BT dose prescription

Dose can be prescribed to Point A, or user defined target volumes. See study handbook for definitions.

8.3.2.5 BT dose reporting

Point A dose will be reported for all patients by all participating centers.

In addition to Point A dose, the centers using 3D imaging may also report the D90 to the Gec-ESTRO defined high risk clinical target volume (HR-CTV). See study handbook for definitions.

8.3.3 Timing and fractionation of LDR & PDR Brachytherapy

Following the completion of whole pelvic RT, the patient will receive an intracavitary implant. The patient may receive LDR intracavitary BT in one or two applications at the discretion of the radiation oncologist. The first insertion should be performed promptly upon completion of whole pelvic RT. If two implants are contemplated, the second implant should be completed within three weeks of the completion of whole pelvic RT, (total treatment time should be less than or equal to 56 days).

8.3.3.1 Total Normal Tissue Tolerances (EBRT + LDR BT)

International Commission on Radiation Units (ICRU)

ICRU 38 Bladder reference point ≤ 75 Gy

ICRU 38 Rectal reference point ≤ 70 Gy

Vaginal Mucosa ≤ 130 Gy

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8.3.4 Timing and fractionation of HDR brachytherapy

HDR brachytherapy may start in week 4, 5 or at the end of external beam radiotherapy. If HDR brachytherapy begins during EBRT, EBRT should not be given on the day of brachytherapy. If brachytherapy starts in week 4, there should be a maximum of one insertion per week. If the brachytherapy starts in week 5 or at the end of EBRT, two insertions per week may be done. This will enable treatment to be completed within eight weeks (EBRT plus brachytherapy). Three to five fractions of HDR brachytherapy are permitted as described in the study handbook.

8.3.4.1 Total Normal Tissue Tolerances (EBRT + HDR BT)

Normal tissue doses should be calculated.

ICRU 38 Rectal reference point $\leq 70 \text{ Gy}_3$ (EQD2 using $\alpha/\beta=3$ for late effects)

ICRU 38 Bladder reference point $\leq 75 \text{ Gy}_3$ (EQD2 using $\alpha/\beta=3$ for late effects)

Vaginal Mucosa $\leq 130 \text{ Gy}_3$ (EQD2 using $\alpha/\beta=3$ for late effects)

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Table 3. HDR- Normal tissue dose constraints. Guideline and examples to dose per fraction of HDR Physical dose per fraction, total physical dose (EBRT+BT) and total dose (EBRT+BT) EQD2

Total EBRT at 1.8 Gy/fx	# HDR fractions	HDR Point A dose/fraction Gy	Maximum physical dose per fx for bladder Gy	Total (EBRT+BT) maximum Physical bladder dose Gy (EQD2 Gy ₃)	Maximum Physical dose per fx for rectum Gy	Total (EBRT+BT) Maximum physical rectal dose Gy (EQD2 Gy ₃)	Maximum Physical dose per fx for vaginal mucosa Gy	Total (EBRT+BT) Maximum physical vaginal mucosa dose Gy (EQD2 Gy ₃)
45	3	8.4	5.9	45+17.7= 62.7 Gy (74.7 Gy ₃)	5.3	45+15.9= 60.9 Gy (69.6 Gy ₃)	10.6	45+31.8= 76.8 Gy (129.7 Gy ₃)
45	4	6.8	5	45+20= 60 Gy (75.2 Gy ₃)	4.5	45+18= 63 Gy (70.2 Gy ₃)	9	45+36= 81 Gy (129.6 Gy ₃)
45	5	5.8	4.3	45+21.5= 66.5 Gy (74.6 Gy ₃)	3.9	45+19.5= 64.5 Gy (70.1 Gy ₃)	7.9	45+39.5= 84.5 Gy (129.3 Gy ₃)
50.4	3	7.5	5.3	50.4+15.9= 66.3 Gy (74.8 Gy ₃)	4.6	50.4+13.8= 64.2 Gy (69.4 Gy ₃)	10.2	50.4+30.6= 81 Gy (129.3 Gy ₃)
50.4	4	6.1	4.5	50.4+18= 68.4 Gy (75.4 Gy ₃)	3.9	50.4+15.6= 66 Gy (69.9 Gy ₃)	8.7	50.4+34.8= 85.2 Gy (129.8 Gy ₃)
50.4	5	5.2	3.9	50.4+19.5= 69.9 Gy (75.3 Gy ₃)	3.4	50.4+17= 67.4 Gy (70.1 Gy ₃)	7.6	50.4+38= 88.4 Gy (128.9 Gy ₃)

As in LDR brachytherapy, every attempt should be made to deliver tumouricidal doses, even if the late responding tissues receive a slightly higher dose.

8.3.5 Total treatment time (EBRT + BT)

The total elapsed time for completion of external beam to the whole pelvis, intracavitary BT, and parametrial / nodal RT shall not exceed eight weeks (56 days).

8.3.6 Radiation therapy quality control and documentation

As part of the radiotherapy quality control carried out by the Imaging and Radiation Oncology Core (IROC), off-site dosimetry audits will be performed.

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Data needs to be submitted for selected cases within 3 months of the patient completing radiotherapy treatment.

8.3.6.1 EBRT:

The first two patients:

Simulation films or digitally reconstructed radiograph (DRRs) (for all treatment fields and phases of treatment including EBRT boosts) from each participating centre will be submitted to the NHMRC CTC or IROC directly.

Portal films verifying the position of the external beam films taken during the first week of treatment will be obtained and submitted to the NHMRC CTC or IROC directly.

If the simulator films/ DRRs are acceptable, then simulator films/ DRRs from every 10th patient will be submitted. If the first two patient simulator films/DRRs are unsatisfactory, then centres will be requested to send more simulator films/DRRs until they are in compliance with the protocol.

8.3.6.2 Documentation requirements EBRT

Field outlines are required for all treatment fields. These should be displayed on the simulation films or DRRs.

Portal films, daily treatment records, treatment plan including isodose distribution through the centre of the treatment volume, and dosimetry calculations. Also submit online a completed External Beam Summary Form (found at <http://rpc.mdanderson.org> under Forms).

8.3.6.3 Compliance Criteria for standard radiation therapy

Per protocol: See section 8.3.1.1 – 12

8.3.6.4 Variation Acceptable:

- Total treatment time up to 67 days.
- External beam dose of 43.6-51.9 Gy
- Boost dose of 10 Gy with total external beam dose \leq 65 Gy
- Total dose to point A as outlined in Tables 1 and 2 +/- 5%

8.3.6.5 Deviation unacceptable

- Total treatment time of more than 67 days
- External beam dose of less than 43.6 or greater than 51.9 Gy
- Boost site that exceeds 65 Gy total external beam dose.
- Total dose to Point A less than or more than 5% of doses outlined in Tables 1 and 2

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8.3.6.6 Brachytherapy:

Simulation films, DRR's or ultrasound views (sagittal, coronal and/or axial reconstructions) for the first intracavitary insertion will be submitted to the NHMRC CTC or IROC directly at the completion of treatment.

Centres are encouraged to provide confirmation of the tandem position within the uterine cavity with either ultrasound imaging, CT or MRI. Such imaging (preferably sagittal) during or after each insertion, should be obtained and submitted to the NHMRC CTC or IROC directly.

8.3.6.7 Documentation requirements Brachytherapy

Simulator films, DRRs or CTs or ultrasound images with applicator in-situ for each intracavitary placement, treatment plan (to include source activities, dwell times, dwell positions and isodose lines). Also submit a completed online Gynecological Brachytherapy Protocol Compliance form (located at <http://rpc.mdanderson.org> under Forms).

8.3.6.8 Compliance criteria for brachytherapy

Per protocol: see sections 8.3.2, 8.3.3, 8.3.4.

8.3.6.9 Variation Acceptable:

Brachytherapy starting in week 4 or 5 of EBRT.

8.3.6.10 Variation unacceptable:

Use of interstitial brachytherapy unless as per 8.3.2.1 due to poor response of the primary tumour to external beam radiotherapy.

8.3.7 Total Dose (EBRT + BT) Specification

Total dose will be a combination of the external beam dose at the midplane and the brachytherapy dose using Point A.

8.3.7.1 Total dose reporting

Doses shall be reported as physical dose received.

EBRT whole pelvis/extended field (i.e. 45 – 50.4 Gy)

Central structures: PT A: EBRT + BT e.g. 45 Gy + 2 x 20.00 Gy = 85 Gy (LDR)

ICRU 38 Bladder reference point: EBRT + BT

ICRU 38 Rectal reference point: EBRT + BT

Vaginal mucosa dose: EBRT + BT

Boosts: Nodal boost: EBRT + nodal boost

Parametrial boost: EBRT + parametrial boost

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8.3.8 Overall Compliance criteria

8.3.8.1

Per Protocol: see sections 8.3.1 – 10, 8.3.2, 8.3.3, 8.3.4.

8.3.8.2 Variation acceptable

- Total treatment completed within 56 days (+20% = 67 days)
- Total dose received to Point A inclusive of EBRT and BT = 80 – 86.4 Gy +/- 5%

8.3.8.3 Deviation unacceptable

- Total treatment greater than 67 days
- Total dose received at Point A less than 76 Gy or greater than 90.7 Gy

If an unacceptable deviation is recorded due to low dose to point A, the investigators will be asked to clarify if image guided brachytherapy was used or not used. If image guided brachytherapy was used, the investigator will be asked to specify the dose received to 90% high-risk clinical target volume (HR CTV). This response will be recorded alongside the point A dose.

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9 ASSESSMENT OF EFFICACY, SAFETY AND PATIENT QUALITY OF LIFE

9.1 *Assessment of Efficacy and Baseline Measures*

All patients will undergo routine baseline investigations including appropriate clinical review, baseline bloods and CT scan as outlined in section 10. A baseline MRI and PET or PET/CT scan should also be performed if available to sites to determine if the patient has PET positive nodal disease and/or corpus uterine invasion (Appendix 3). CT and/or MRI results should be used to determine RECIST 1.1 measurements. It is recommended that PET scans are performed in accordance with the standard operating procedures recommended by the American College of Radiology Imaging Network (ACRIN) at:

<http://www.acrin.org/CORELABS/PETCORELABORATORY/PETSOPS/tabid/484/Default.aspx>

In consenting patients, (optional) baseline biopsy samples and a sample of whole blood and plasma will be stored at the site for future translational studies. In addition, at suitable sites patients requiring another biopsy for clinical reasons (such as confirmation of diagnosis) will be asked to consent to donate fresh frozen tissue for planned translational research studies.

Patients will be followed weekly during chemo-radiation and 3 weekly during adjuvant chemotherapy with routine clinical review, toxicity grading and bloods. Patients will be followed up every 3 months for 2 years, and then 6 monthly to 5 years. All follow-up time points are calculated from the date of randomisation. Each patient is planned to complete the study treatment unless disease progression occurs or toxicity prohibits further therapy. Regardless of whether the treatment is completed, each patient will be followed quarterly for two years and then every six months for three additional years or until death. Following completion of all study treatment, response to treatment will be determined by clinical examination and CT chest/abdomen/pelvis result (or MRI if this was used for baseline RECIST measurements) performed 6 months post randomisation according to RECIST 1.1. A PET scan, or preferably PET-CT should be repeated at 4-6 months post completion of chemo-radiation if available to the site. A CT scan should also be performed at the time of any relapse, in order to determine the patterns of relapse seen. Progression free survival (PFS) is defined as the time from randomisation to disease progression as determined by the investigator or death from any cause. Overall survival is defined as the time from randomisation until death from any cause.

9.2 *Assessment of patient quality of life*

Five questionnaires with proven validity and reliability will be used at the follow-up time-points specified in section 10 (Appendix 2). General quality of life will be measured with European Organization for Research and Treatment of Cancer (EORTC) Core questionnaire (QLQ-C30)⁵⁰. It is a cancer-specific questionnaire with 30 items which summarize as five functioning scales (physical, cognitive, emotional, social and role functioning), a global health status/quality of life scale, three symptom scales (pain, fatigue and nausea/vomiting), and six single items assessing additional symptoms and perceived financial impact. To evaluate specific symptoms occurring after radiation

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therapy and chemotherapy we will use the EORTC cervix cancer module (CX24)⁵¹ and a subset of measures from the ovarian cancer module (OV28)⁵². The measures to be used from the OV28 will be: items 31-37 to measure abdominal and gastrointestinal symptoms, items 38-40, 43-45 and 47 to measure chemotherapy side-effects, and items 52-54 to measure attitude to disease and treatment⁵². Together the CX24 and OV28 will provide the following summary scales: symptom experience, abdominal/gastrointestinal symptoms; other chemotherapy side-effects; hormonal/menopausal symptoms; body image/attractiveness; attitude to disease and treatment; vaginal/sexual function and lymphoedema^{51,52}. In addition, two questions from the EORTC prostate cancer module (PR25) have been added to assess limitations to daily activities caused by urinary (Q39) and bowel (Q40) problems. As psycho-sexual health is a particular focus in this study, we will also use the Sexual function-Vaginal Changes Questionnaire (SVQ)⁵³. Ten of its items are applicable to all patients, summarising as three scales (intimacy, sexual interest and global sexual satisfaction). A further ten items for sexually active respondents provide an additional two scales: vaginal changes and sexual functioning. In addition, the reliable and validated FACT/GOG neurotoxicity 4 item subscale will be used to specifically assess for the impact of any peripheral neuropathy seen in the trial⁵⁴. A standardised checklist will be used to capture reasons for non-completion of the quality of life questionnaires. If a quality of life questionnaire is not available in a language that the patient can complete then it should be omitted. Questionnaires should not be completed using an interpreter.

The quality of life data will be used to determine the following objectives and test the related hypotheses.

OBJECTIVES

1. To determine the prevalence of women in each arm reporting long-term symptom issues after treatment as measured by the symptom-specific subscales of the measures.
2. To determine the duration of any patient-reported long-term symptom issues in each arm.
3. To measure the long-term impact of treatment on psycho-sexual health in each arm.
4. To correlate the scores obtained from the various sub-scales with global quality of life.
5. To correlate the scores obtained from the various symptom sub-scales with toxicity as measured by the physician using CTCAE v4.0.
6. To identify subsets of women at greater than average risk of long-term symptom issues or impairments in psychosexual health who could be targeted in the future for supportive care interventions.

HYPOTHESES TO TEST

1. That a significant component of women in both arms will report long-term problems with bowel, bladder and psycho-sexual function that impact on quality of life.

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2. That patients in the adjuvant chemotherapy arm will have a short-term detriment in quality of life (with particular impacts on fatigue and neurotoxicity), but that this returns to be similar to the control arm by about a year.
3. That patients will report more toxicity issues using the patient reported outcome measures than clinicians using the CTCAE v4.0.
4. That particular subsets of women will have more QOL detriment than average e.g. those who are sexually active, pre-menopausal or single at baseline.

9.3 Assessment of Safety

9.3.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

AEs must be reported as AEs even if they do not meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the subject is at risk of death at the time of the event),

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- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

- (i) The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- (ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Subject Information Sheet and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010)).

An event is causally related if there is a reasonable possibility that the intervention caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

For the purposes of this study, the following adverse events are not reported as SAEs:

- Hospitalisations related to disease progression
- Administration of chemotherapy; or
- Administration of a study procedure; or
- Unrelated scheduled elective surgery; or
- Convenience purposes, e.g. transportation difficulties, timing of blood transfusion

9.3.2 Reporting of Serious Adverse Events (including SUSARs)

The investigator is responsible for reporting all Serious Adverse Events (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 1 working day of the investigator becoming aware of the event using the SAE form. SAEs must be reported up to 30 days from the end of study intervention.

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SAE reports should be reported to the CTC as per the procedure documented in the Study Manual.

For the purpose of this study, SAEs occurring prior to commencement of study treatment do not need to be reported.

The CTC will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The CTC will be responsible for providing reports to the Lead HREC.

The investigator must notify the local HREC as required.

The study sponsor/CTC will submit 'reportable safety events' to the TGA in Australia and to national coordinating centres to provide to the regulatory authorities in other participating countries for which the CTC is responsible.

The following information will be recorded for each Serious Adverse Event:

- Event description including classification according to NCI CTCAE
- Primary and secondary diagnoses of event (If death/hospitalisation)
- Severity / Worst Grade
- Attribution to study intervention
- Expectedness (listed in IB/product information)
- Action taken with study intervention
- Impact of SAE (e.g. hospitalisation details)
- Outcome of SAE including end date if recovered

9.3.3 *Pregnancy*

In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. Pregnancies occurring up to 6 months after the completion of the study must also be reported to the investigator. The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The NHMRC Clinical Trials Centre must be notified within 1 working day using the SAE form and the subject followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal.

10 SCHEDULE OF ASSESSMENTS

Checklist for investigators at baseline, treatment and follow up ^A:

	All follow-up time points are taken from the date of randomisation					
	Baseline ^B (Before Randomisation)	During Chemoradiation Week 0 - 5	Adjuvant Chemotherapy (Arm B only) Every 3 weeks: before each cycle of treatment	End of Treatment ^{C, I}	3 - 24 months: ^J every 3 months	24 - 60 months: ^J every 6 months
Medical history and demographics	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X
Pelvic exam	X	If clinically indicated		If clinically indicated	X	X
Assessment of toxicity		X	X	X	X	X
Performance status (ECOG)	X		X	X		
Weight	X		X	X	X	X
Height	X					
Chest/abdominal/pelvis CT	X ^E				X ^D	If clinically indicated ^D
PET scan (if available)	X ^E				X ^F	
MRI (pelvis)	X ^E				X ^E	
Tumour assessment by RECIST 1.1	X				X ^{D, E}	
Full blood examination (WCC, ANC, Hb, Platelets)	X	X	X	X	If clinically indicated	

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Electrolytes (Na, K, Mg, Ca, PO4)	X	X	X	X	If clinically indicated	
Serum creatinine	X	X	X	X	If clinically indicated	
Creatinine clearance (Cockcroft-Gault)	X		X			
Bilirubin, Alk Phos, ALT, AST	X		X	X	If clinically indicated	
Pregnancy test	If clinically indicated					
HIV test	If clinically indicated					
Quality of Life questionnaires (EORTC QLQ C30, CX24, OV28, FACT, SVQ)	X		X	X	X	X ^G
Biopsy sample & blood sample (if consented to translational research component)	X ^H					

^A Follow-up time points start from the date of randomization (not from conclusion of therapy). Patients in Arm A can omit the 3 month follow-up visit, if this time-point will be assessed as part of the completion of treatment visit. Patients in Arm B can omit the 3 month follow-up visit as this will fall into the treatment period. Patients in Arm B can omit the 6 month follow-up if this time-point will be assessed as part of the end of adjuvant chemotherapy treatment visit.

Follow-up visits should be scheduled +/- 2 weeks of the calculated follow-up time point.

^B Baseline assessments should occur within 6 weeks of randomisation. Estimate of tumour size at clinical pelvic examination should be documented. Treatment should start no more than 6 weeks after randomisation. Baseline demographic assessment should include recording of race and smoking status (smoker, non-smoker [less than 100 cigarettes in lifetime], ex-smoker [quit smoking more than 1 year ago]). Of note any required blood tests may

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be taken on or up to 72 hours prior to the date of baseline assessment. If baseline bloods are taken within one week prior to start of treatment then they do not need to be repeated prior to the start of treatment.

^C Review at approximately 4 weeks post completion of all study treatment

^D To be performed once at 6 months post randomisation and then repeated if relapse clinically suspected

^E Both MRI and PET scan should be performed at baseline if available to the site. Only MRI or PET/CT results (not PET alone) should be used to determine nodal status for the purposes of stratification/randomisation. If the patient has had both a routine PET/low-dose CT and MRI pelvis then a separate CT chest/abdo/pelvis is not required. In this situation, MRI rather than CT should be repeated once only at 6 months post randomisation in order to obtain RECIST measurements. The MRI should also be repeated at 6 months if the baseline MRI was the imaging modality used for RECIST measurements.

If the patient has had a routine PET/low-dose CT at baseline but no MRI pelvis then a separate CT chest/abdo/pelvis is required both at baseline and 6 months post randomization. However, if CT component of the PET was done using full IV contrast and is considered suitable to perform RECIST measurements, then a separate CT chest/abdo/pelvis is not required. Refer to Appendix 6 for information requirements for PET reports.

^F PET scan (preferably PET/CT) to be repeated (if available to the site) once only at 4 - 6 months post completion of chemo-radiation (for both arms). Refer to Appendix 6 for information requirements for PET reports.

^G Quality of life questionnaires to be completed out to 36 months post randomisation. Quality of life questionnaires do not need to be completed once a patient has relapsed or is diagnosed with a 2nd primary cancer. If a quality of life questionnaire is not available in a language that the patient can complete then it should be omitted. Questionnaires should not be completed using an interpreter.

^H In patients consenting to the translational component of the study, a sample of tumour, blood for DNA and plasma will be collected for future translational studies. Refer to the study handbook for additional information about how these specimens should be collected and stored.

^I If the assessment for the end of treatment visit coincides (+/- 2 weeks) with the 3 or 6 month follow-up visit, then only one visit is needed where data for both end of treatment and follow-up is collected.

^J Post disease progression patients should be followed for survival and details of anti-cancer treatments given should be recorded.

11 STATISTICS

This is a Phase III trial examining the impact of 4 cycles of carboplatin and paclitaxel as adjuvant treatment after initial concurrent chemoradiation for patients with locally advanced cervical cancer suitable for curative therapy. The questions addressed by this study are the effect of adjuvant chemotherapy post chemo-radiation on overall and progression-free survival. The primary outcome of the study is overall survival.

11.1 Sample Size

The overall trial sample size has been planned to ensure sufficient power for demonstrating an overall survival advantage of chemo-radiation and adjuvant chemotherapy compared with chemo-radiation alone. The expected 5-year overall survival rate for this population is approximately 60% - 65%, based on the pivotal studies included in the MRC individual patient data meta-analysis¹². An absolute reduction in mortality of at least 10% would be considered clinically worthwhile. However, it is anticipated that the cohort of patients recruited into this trial is likely to be at a lower risk than the cohorts in the published meta-analysis. Thus a control 5-year rate would be closer to 70-75%. Based on an exponential distribution, the table below shows the sample sizes required for different mortality reductions based on 95% confidence and 80% power, a minimum of a 48 month accrual period and a minimum of 42 months follow-up. Rather than adjust directly for non-adherence, the difference margin has been reduced to 8% to allow for a modest dilution due to drop-outs (patients allocated to receiving adjuvant chemotherapy arm but then not receiving the treatment)

OS at 5 years (%)	Total sample size	Hazard ratio
70 vs 78	874	0.70
72 vs 80	828	0.68
73 vs 81	804	0.67

Table is based on a 8% margin with 100% adherence

Based on this table, a total sample size of 900 (450 per arm) will have 80% power with 95% confidence of detecting a reduction in the hazard of death of at least 32% (hazard ratio 0.68) from the control regimen (approximate 8% improvement in overall survival at 5 years from 72% to 80%) and allowing for some lost to follow-up and a further 4% cross-over rate. Additionally, this sample size will have > 80% power to detect a 10% survival difference (after accounting for non-adherence) if the control rate is marginally higher (75%), or lower (70%). The expected event rate at the completion of the study is 234 deaths.

11.2 Statistical Analysis

Effectiveness analyses will be performed on an intention to treat basis and toxicity analyses by treatment received. All comparisons will be 2-tailed and death from any cause will be considered as an event. Nominal significance levels will be 0.05 for comparison of overall and progression

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free survival. Primary time-to-event analyses will be described with Kaplan-Meier curves and unadjusted logrank tests. Exploratory multivariable modelling will be performed adjusting for baseline levels of key prognostic factors using proportional hazards or other appropriate regression models. The proportion of patients achieving a complete or partial tumour response in each treatment group will be compared with either chi-squared or exact tests (conditional binomial exact test). Results will be provided with estimates and confidence intervals where feasible. Specific sub-group analyses will be performed to assess if the effect of treatment differs according to the treatment received or stratification variables, i.e. nodal involvement, clinical tumour stage and age. An exploratory analysis of the impact on outcome of the presence of uterine corpus invasion on baseline MRI will also be performed.

Quality of life assessments: All patients with a valid baseline and at least one follow-up QOL questionnaire will be included in the analysis. QOL will be collected every 3 months in the first two years and every 6 months in the third year until disease progression or 36 months from randomisation. To evaluate the differences between the treatment groups with respect to the effect of treatment burden on life-quality during and up to 3 years after treatment, the summary scales from the QLQ-C30, CX24/OV28, FACT and SVQ will be modelled using regression and other appropriate statistical methods.

We plan to collect quality of life data on all patients able to complete one of the currently available translations of the questionnaires. For the EORTC measures a sample size of 550 patients with quality of life data will provide over 90% power to detect a 10 point difference on a 100 point scale with standard deviation of 30 points and using a notional significance level of $2p < 0.01$ to account for the multiple comparisons^{55,56}.

11.3 Secondary endpoint: Progression Free survival

Progression free survival (PFS) is defined as the time from randomisation to the time of disease progression as determined by the investigator (by clinical, radiological or pathological means) or death from any cause. Patients without an event prior to the study close-out date will be censored at the study close-out date or at the date of last contact if the patient is lost to follow-up. If a patient receives a subsequent anti-cancer therapy without prior documentation of disease progression, the patient will be censored at the date the patient was last seen for tumour assessment before starting the new anti-cancer therapy.

11.4 Definition of study populations for analysis

- The primary analysis population for the primary efficacy endpoints will be based upon the intention to treat (ITT) principle population, while a sensitivity analysis will be undertaken on the evaluable population. Secondary efficacy endpoints will be reported for the ITT population only. The ITT principle calls for the analysis of all patients randomised to the treatment group originally allocated regardless of which treatment regimen the patient actually received.

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- Safety population: All randomised patients who receive at least 1 dose of study treatment. The primary safety analysis will be based on an all patients treated. Patients are counted in the group according to the treatment they actually receive.

11.5 Interim analysis

For efficacy: At the end of the study, approximately 220 deaths are expected after 3-years of follow-up. A formal interim analysis for efficacy is planned after a total of 120 deaths have been observed in the study. Comparisons will be performed at the nominal significance level $2p=0.003$ based on the O'Brien-Fleming boundary to preserve an overall type I error probability of no more than 0.05. If this boundary is crossed, consideration will be given to stopping the trial. Any such decision would also take into consideration the maturity of the data (in terms of median follow-up etc.) and not necessarily just that the stopping boundary has been crossed.

For futility: An interim analysis for futility is planned using the PFS rate, as this is a major secondary end-point that will have a higher event rate than overall survival. The secondary endpoint is PFS and it is anticipated that after 3-years the PFS rate in the control arm will be approximately 65%, based on pivotal studies included in the MRC individual patient data meta-analysis¹², while the rate in the intervention arm is expected to be 75%. However, patients not relapsing before 3 years could be considered as having a negligible risk of relapsing (i.e. cure) and for those who do relapse; their median time to relapse is approximately 12 months. Based on a Gompertz survival distribution, at the end of the study, a total 235 patients would be expected to progress after 3 years of follow-up. A relative reduction in PFS of less than 13% (HR 0.87, absolute benefit of 3.8%) would not be considered sufficient to change clinical practice and the study would not be considered as demonstrating a clinically worthwhile benefit. An interim analysis after 70% of the information is available (after 165 patients have progressed) corresponds to a futility boundary for the HR of 0.89 (and an estimated HR of 0.99). If after 165 progressions have been observed, the lower 95% CI is greater than 0.89, the study will be considered futile to achieve its target benefit⁵⁷.

The interim analyses will be reported to an Independent Safety and Data-Monitoring Committee (IDSMC) who will advise the trial steering committee on the safety and feasibility of the study. There will be regular monitoring of the study for safety by an Independent Safety Data Monitoring Committee (IDSMC) who will review the safety profile of the patients in the trial and make recommendations to the trial steering committee.

Consideration will be given to modifying the treatment or stopping the trial early based on the reports of the IDSMC if:

- a) The efficacy or futility boundaries are crossed in the formal interim analyses outlined above triggered by the number of events (progressions, deaths);
- b) a clearly more effective therapy becomes available.

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c) the toxicity appears to be excessive

The toxicity would be considered excessive if during the carboplatin and paclitaxel chemotherapy treatment there is a significantly higher than expected rate of life threatening neutropenic sepsis or grade 4 peripheral neuropathy than would be expected when carboplatin and paclitaxel is used to treat ovarian cancer. Toxicity rates will be formally evaluated after 60 (approx 30 per arm) and 150 (approx 75 per arm) patients have completed all study treatment. This is expected to be approximately 7 months after the 60th and 150th patients have been randomised. The goal of these interim evaluations of toxicity is to ensure that there is not an excessive rate of neurological or haematological toxicity in the intervention arm.

Expected toxicities of peripheral neuropathy and febrile neutropenia are estimated to be at most 15% (grade 3 and 4) in the intervention (adjuvant chemotherapy) arm. These rates will be specifically considered by the IDSMC and it is envisaged that if the rate of these toxicities in the adjuvant chemotherapy group (Arm B) greatly exceeds the rate of toxicity experienced in the standard care group (Arm A) (eg. by more than 25% meaning that the 95% one-sided confidence interval for the difference in the rates includes a 25% detriment), then consideration will be given to dose adjustment or stopping the study based on the oversight and advice of the IDSMC.

12 STUDY STRUCTURE

ANZGOG will be the lead group for this GCIG study, in collaboration with the NHMRC CTC, University of Sydney which is the coordinating centre for the trial. The Principal Investigator and the NHMRC CTC are responsible for the day to day running of the trial as detailed in trial handbook and local standard operating procedures. The NHMRC CTC will in addition prepare reports for the Trial Management Committee (TMC), TMC Executive and IDSMC, including interim analysis, and will make safety and progress reports to the Ethics and Regulatory authorities and to GCIG groups for their regulatory and ethics requirements as needed. The TMC will include a representative from each participating cooperative group and country. The TMC will meet by teleconference as required and will aim to meet face-to-face at least once per year. The TMC responsibilities include protocol development, study planning, monitoring and progress, review of serious adverse events. A TMC Executive Committee who would meet on a more frequent basis may be selected from the TMC in order to expedite decision-making and would be led by the Principal Investigator.

In addition, the TMC has responsibilities to all study sites in taking all reasonable steps to ensure the proper conduct of the study as regards ethics, protocol adherence, integrity and validity of the data recorded on the case report forms.

An Independent Data Safety Monitoring Committee (IDSMC) will be appointed by the TMC and consist of a minimum of an independent medical oncologist, radiation oncologist and statistician.

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This committee will undertake reviews of all collected patient data at specified time points during the study to assess safety aspects of the study regimens.

13 ADMINISTRATIVE ASPECTS

13.1 Ethics and regulatory compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC National Statement on Ethical Conduct in Human Research (© Commonwealth of Australia 2007) and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004. The investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.

13.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney and will only be available to staff directly involved with the study.

13.3 Protocol amendments

Changes and amendments to the protocol can only be made by the Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial subject(s).

13.4 Data Handling and Record Keeping

Trial data will be recorded on the (e-)CRFs provided. All required data entry fields will be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a subject's medical records, hospital charts, clinic charts, the investigator's subject study files, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a subject's study-related data.

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All study-related documentation will be maintained for 15 years following completion of the study or according to local regulatory requirements.

13.5 Study Monitoring

Data from this study will be monitored according to the study monitoring plan. In Australia and New Zealand sites will be monitored by Clinical Trials Program staff from the NHMRC Clinical Trials Centre (NHMRC CTC). For international sites monitoring will be the responsibility of the National Coordinating Office. Monitoring will include centralized review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites for source data verification, review of the investigator's site file and drug handling records. The monitoring staff will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the subject gives authorized monitoring staff direct access to their medical records and the study data.

13.6 Audit and Inspection

This study may be subject to audit or inspection by representatives of ANZGOG or the NHMRC CTC), or representatives of regulatory bodies (e.g. Therapeutic Goods Administration).

13.7 Clinical Study Report

A Clinical Study Report will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to relevant grant funding bodies, all investigational sites, as well as submitted to HRECs.

13.8 Publication Policy

The Trial Management Committee will appoint a Writing Committee to draft manuscripts based on the trial data. Manuscripts will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol using the study group name, with subsequent publications of data subsets. The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication, in accordance with the ANZGOG publication policy.

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15 LIST OF APPENDICES

Appendix 1. Participant information and consent forms for ANZGOG sites

[HOSPITAL LETTERHEAD]

PARTICIPANT INFORMATION AND CONSENT FORM

A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally-advanced cervical cancer compared to chemoradiation alone

THE OUTBACK TRIAL



Principal Investigator: [name of site principal investigator]

The sponsor for this study in Australia and New Zealand is the University of Sydney. We are inviting you to join this clinical research study because you have been diagnosed with cervical cancer (cancer of the cervix). This Participant Information Form contains detailed information about the research study. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in the study before you decide whether or not to take part in it.

Please read this Participant Information Form carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the study with a relative or friend or your local health worker.

Once you understand what the study is about and if you agree to take part in it, you will be asked to sign the Patient Consent form. By signing the Patient Consent Form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Patient Consent Form to keep as a record.

1. What is the purpose of this study?

The standard treatment for the type of cervical cancer you have is currently radiotherapy combined with chemotherapy (chemo-radiation). Radiotherapy to the pelvis destroys potential cancer cells in the pelvic area and significantly reduces the risk of tumour recurrence in the pelvic area. Giving chemotherapy using a drug called Cisplatin during radiotherapy has been shown to increase its effectiveness and is part of standard treatment.

Studies among patients with other cancer types have shown that the addition of more chemotherapy after chemo-radiation reduces the risk of tumour recurrence at other places in the body. This has not yet been established for cervical cancer patients. Giving additional chemotherapy after initial standard treatment is known as 'adjuvant chemotherapy'.

The objectives of this trial are to find out whether adjuvant chemotherapy (using two other drugs) after chemo-radiation will increase the chances of survival and reduce the risk of tumour recurrence in the pelvis and other places. The risk and severity of

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side effects and quality of life during and after treatment will also be evaluated and compared. This trial will help the researchers understand the safety and effectiveness of the treatment.

In this trial one group will receive standard chemo-radiation alone, whereas the other group will receive standard chemo-radiation and then additional chemotherapy.

One of the chemotherapy drugs used in this study, paclitaxel, is not currently registered in Australia for use in the treatment of cervical cancer but is registered and commonly used for the treatment of other cancers such as breast and ovarian cancer. It is also available and commonly used in many other countries for the treatment of secondary cervical cancer. The other two chemotherapy drugs used, cisplatin and carboplatin, are part of standard treatment for cervical cancer. The drug paclitaxel is being supplied by Hospira for patients in this study in Australia.

The institution/hospital where you are being treated will be paid a nominal amount to cover their costs related to your participation in the study. The sponsor and the investigator do not have a financial interest in the outcome of this study.

A total of 900 women will participate in this study from Australia, New Zealand and other countries.

2. Why have I been asked to participate in this study?

You have been asked to join this study because you have been diagnosed with cervical cancer, which is locally-advanced and therefore not suitable for surgery. Chemo-radiation is the standard treatment for the type of cervical cancer you have and will be given to all women in this trial.

You have been asked to take part in this clinical trial, to try to find out if extra chemotherapy after the standard chemo-radiation, will reduce the possibility of the cancer returning,

If you choose not to take part in this study, the alternative is that your doctor would treat you with chemo-radiation as per standard therapy.

3. What if I don't want to take part in this study, or if I want to withdraw later?

Participation in this study is voluntary. It is completely up to you whether or not you wish to participate. Your choice not to participate will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

Before you make your decision, the Investigator or a member of the study team will be available so you can ask any questions you have about the study. You can ask for any information you want. Please sign the Patient Consent Form only after you have had a chance to ask your questions and have received satisfactory answers. New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may impact on your willingness to continue in the study.

You may withdraw from this study at any time. There is a difference between withdrawing from the study treatment and withdrawing from the study entirely. If you decide to withdraw, please notify a member of the research team beforehand. This notice will allow your doctor to inform you if there are any health risks or special requirements linked to withdrawing.

If you decide to discontinue the study treatment, you will be asked to attend follow-up visits to allow collection of information regarding your health status. Alternatively, the investigator/sponsor will request your permission to access your medical records for collection of follow-up information for research and analysis.

In the event that you withdraw from the study entirely, the effective date of the notification will be the date on which your withdrawal is received by the OUTBACK

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study team. No information about you will be collected from that point in time onwards but any information collected about you prior to that date can be used and forms part of this study.

Your study doctor may withdraw you from the study if he/she does not think it is in your best interest to continue or if you are unable to complete the study procedures.

4. What does this study involve?

If you decide to participate in this study you will be randomly assigned by a computer to one of two groups. Neither you nor your doctor will be able to choose which group you are assigned to.

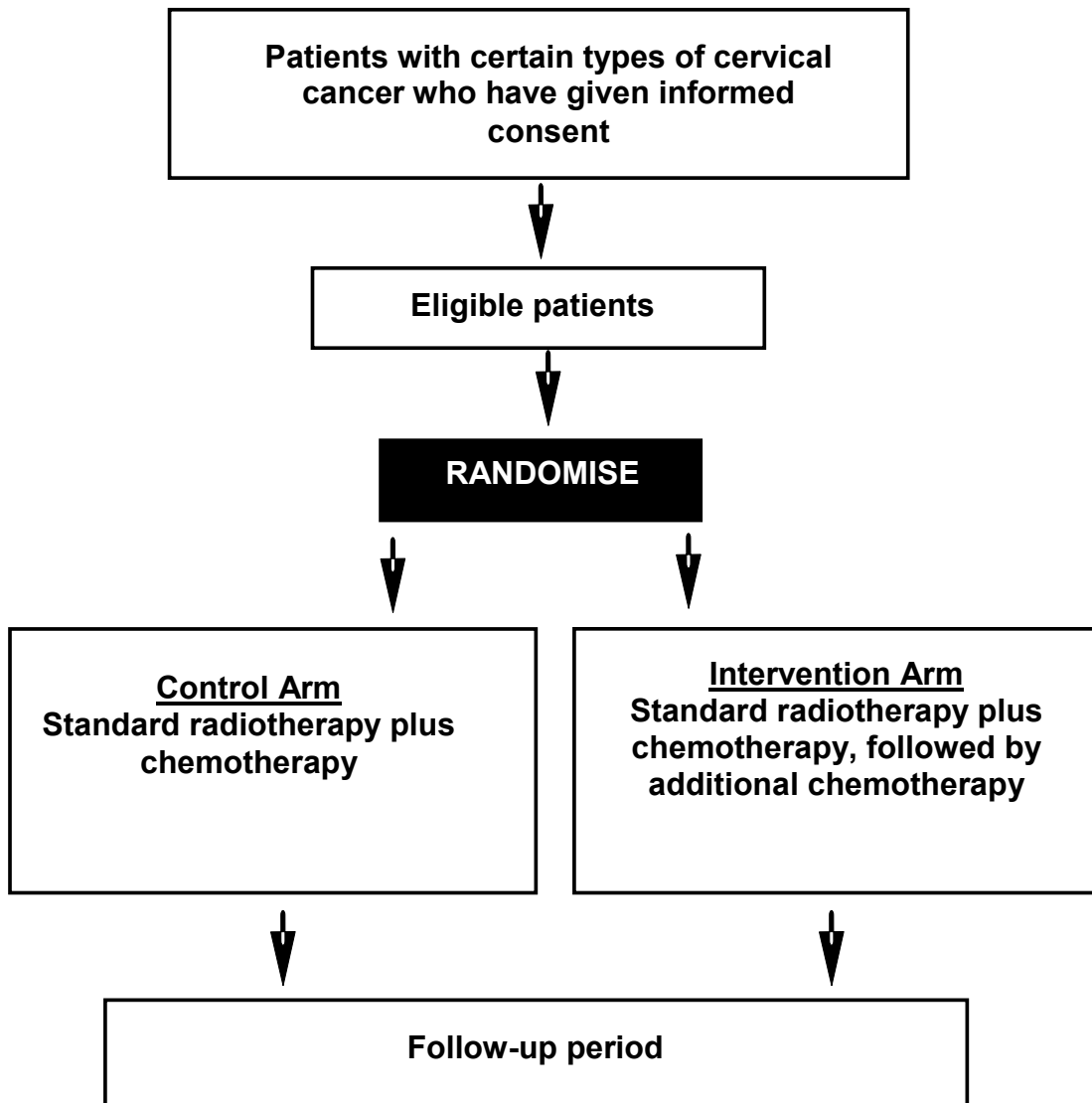
The researchers want to compare the effect on survival, any side effects this treatment may cause and the effect of this treatment on your quality of life compared to the standard treatment.

Control Arm: This group will receive the current standard treatment for this type of cancer and side effects and quality of life information will be collected to compare with the intervention group. This group will receive chemo-radiation (standard radiotherapy plus cisplatin chemotherapy) only.

Intervention Arm: This group will receive the treatment that involves more than the standard treatment for this type of cancer. This group will receive chemo-radiation (standard radiotherapy plus cisplatin chemotherapy), followed by carboplatin and paclitaxel chemotherapy.

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Study Schema



Study Treatment

Before starting the study treatment there will be a baseline assessment which includes the following: medical history, physical examination, weight, pelvic examination, blood tests and scans (CT scan for everyone plus a MRI and PET scan if this is available through your treatment centre).

If clinically indicated there may be a pregnancy test to exclude pregnancy.

The chemo-radiation treatment will take up to 6 weeks and is given to all patients. It consists of external beam radiotherapy, given 5 days per week and an intravenous infusion of the chemotherapy drug cisplatin given on one day of the week during the radiotherapy treatment. Following external beam radiotherapy, internal radiation (brachytherapy) will be administered. This involves placement of a radioactive source into your uterus, cervix and vagina for a specific period of time, after which the radioactive source will be removed. Chemo-radiation including brachytherapy is part of the standard

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treatment given to all patients. Your radiation oncologist will explain in detail about your brachytherapy timing and number of treatments.

If you are randomised to the intervention group, after the chemo-radiation (including brachytherapy) treatment has been completed and you have recovered from any side-effects (after approximately four weeks), you will be given four further infusions of carboplatin plus paclitaxel chemotherapy. Prior to this chemotherapy you will also receive a pre-medication to prevent an allergic reaction or other side effects. The chemotherapy will be given on one day every three weeks. It will take approximately six hours to give the carboplatin plus paclitaxel chemotherapy. You will not be able to drive yourself home after chemotherapy, as the pre-medication can make some patients slightly drowsy.

If you are in the intervention group, receiving the additional chemotherapy you will need to give 4 more blood samples (2 teaspoons per sample) than would normally be taken, to check your blood results prior to the additional chemotherapy treatments. There will also be four extra hospital visits for the chemotherapy to be given after your radiotherapy has been completed.

For all patients in the trial, after completion of treatment the study doctor will assess how your cancer has responded. This assessment will include a physical and pelvic examination and blood tests. A CT scan (and a PET scan if available) will be repeated 4 – 6 months after completion of the chemo-radiation. You will continue to be seen by the study doctor once every three months for the first two years, and once every six months for three more years. These follow up visits will include a physical and pelvic examination.

You will be asked to fill in short questionnaires about your quality of life before you start treatment, after completing chemo-radiation and (if applicable) after the additional chemotherapy has been completed. You will also be asked to complete the questionnaires every 3 months during the first 2 years of follow-up after treatment and then every 6 months in the third year. These questionnaires will assist the team to find out how you are feeling in yourself and the effect treatment has upon you and your daily activities. These questionnaires should take about 30 minutes to complete. If you agree to participate in this study, you will be asked to sign the Patient Consent Form.

5. Are there risks to me in taking part in this study?

Medical treatments often cause side effects. You may have none, some, or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your doctor. Your doctor will also be looking out for side effects. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. The researchers don't know whether giving the additional chemotherapy treatment in this study might increase the chance of you getting short or longer-term side effects.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your doctor may need to stop your treatment. Tell your doctor if you have any problems. Your doctor will discuss the best way of managing any side effects with you.

General side effects of radiotherapy (part of standard of care treatment):

The side-effects of radiation may include any, all or none of the following.

Common side-effects (in more than 1 in 10 patients)

- Diarrhoea

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- Burning or pain when passing urine
- Bowel cramps or abdominal pain
- Tiredness
- Loss of appetite
- Loss of pubic hair
- Menopause: Radiotherapy may cause your ovaries to stop working permanently. If you haven't already been through menopause you may experience menopausal symptoms such as hot flushes

Less common side-effects (in more than 1 in 20 patients)

- Reddening, itching or in some cases blistering of the skin and other tissues in the pubic area which is exposed to the radiation beam
- Nausea or vomiting
- Effect on the vagina: Some women experience mild vaginal irritation and discharge during and shortly after treatment. Radiotherapy may also cause internal scar tissue to form, which sometimes shortens and narrows the vagina. These changes can be prevented or minimised with the use of a vaginal dilator (also called a vaginal cylinder) which your treatment team will instruct you to use.

Most of these side-effects can be controlled with medication and will usually get better when the radiation is completed. Rarely (in less than 1 in 10 patients), radiation may cause some permanent damage to the small or large intestine, rectum, ureter, bladder or lymph nodes in the pelvic area causing swelling of the legs which is known as lymphoedema. Sometimes complications from the brachytherapy treatment can also result in damage to the uterus, which generally gets better without the need for specific treatment. These problems may require medication such as antibiotics or very rarely hospitalisation or a surgical procedure to repair or manage. Very rarely (in less than 1 in 1000 patients), nerve damage may occur which may cause numbness or weakness in the legs.

General side effects of chemotherapy:

The most common general side-effects of chemotherapy include tiredness, nausea and vomiting (which is usually minimal with standard anti-nausea medication), mouth sores, loss of appetite and taste changes. Blood counts (white blood cells, red blood cells, and platelets) and electrolyte salts (sodium, potassium, magnesium) may also be lowered. A decrease in these blood counts may increase your risk of infection, fatigue, and abnormal bleeding.

Prior to chemotherapy you will be given a pre-medication which can help with some of the side-effects. You will also be given some medication to take at home after treatment to help prevent and manage any nausea and vomiting. These medications can sometimes cause temporary problems with headache, constipation and trouble sleeping.

Cisplatin is the drug that is given during chemo-radiation as part of standard therapy for your cancer. Common side effects (in more than 1 in 10 patients) include tiredness, and nausea. Less commonly it may cause damage to your kidneys (less than 1 in 100 patients), which may rarely be permanent. In order to prevent this extra fluid is given into a vein with the treatment and you will also be advised to increase your fluid intake by mouth. In addition a close eye will be kept on kidney function with regular blood tests before each treatment. Less common side effects (less than 1 in 100 patients), which may rarely be permanent, include ringing in the ears or some

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loss of hearing, problems with balance, or numbness and tingling in the fingers or toes. Development of blood clots can also occur rarely, in part because the cancer may pre-dispose to this.

Carboplatin is one of the two drugs that will be given after your chemo-radiation if you are in the intervention group. It is similar to cisplatin but side effects are generally less marked.

Common (in more than 1 in 10 patients)

- Lowering of blood counts leading to an increased risk of infection, bleeding or need for a blood transfusion
- Nausea
- Taste changes
- Tiredness (fatigue)

Uncommon (in less than 1 in 10 patients)

- Sores in the mouth
- Kidney damage, which is usually reversible
- Nerve damage such as numbness and tingling in the hands and feet that in more severe cases can lead to difficulty walking or buttoning clothes. This may take many months to resolve after chemotherapy is completed and rarely can be permanent.

Rare (in less than 1 in 100 patients)

- Hearing damage, which is very rarely severe or permanent

Paclitaxel is the second of the 2 drugs given after your chemo-radiation if you are in the intervention group. It does cause hair loss which starts 2 -3 weeks after the first dose. It is, however, temporary and your hair will start to re-grow about 3-6 weeks following treatment. As well as losing the hair on your head there will be thinning of your eyebrows, eyelashes and other body hair.

Common (in more than 1 in 10 patients)

- Lowering of blood counts leading to an increased risk of infection, bleeding or need for a blood transfusion
- Hair loss
- Tiredness (fatigue)
- Nerve damage such as numbness and tingling in the hands and feet that may lead to difficulty walking or buttoning clothes. This may take many months to resolve after chemotherapy is completed and rarely can be permanent.
- Muscle and joint aches
- Constipation

Uncommon (in less than 1 in 10 patients)

- Sores in the mouth
- Abnormalities in the heart rate such as a slow regular pulse which is not harmful
- Nausea
- Diarrhoea
- Liver blood test abnormalities
- Allergic reactions causing hives, wheezing and low blood pressure

Rare (in less than 1 in 100 patients)

- Temporary visual disturbances such as the sensation of flashing lights or blurred vision
- Serious abnormalities of the heart rhythm
- Seizures

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It is important that women participating in this study are not pregnant and do not become pregnant during the study as the study procedures may damage an unborn baby. If you are a woman of childbearing age and there is any possibility that you are pregnant, your doctor will need to perform a urine pregnancy test before you start in the study. If necessary, you should use reliable contraception (such as oral or implanted contraceptive or an IUD) during the course of the study. If you think you may be pregnant, it is important to let your doctor know immediately.

Your treatment may cause temporary or permanent sterility. Please discuss this with your doctor if you have any concerns about future fertility.

6. What happens if I suffer injury or complications as a result of the study?

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. Treatment for the injury or complication will be provided free-of-charge at a public hospital.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is sufficiently serious and is caused by unsafe drugs or equipment, or by the negligence of one of the parties involved in the study (for example, the researcher, the hospital, or the treating doctor). If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

You do not give up any legal rights to compensation for your injury or compensation by participating in this study. If you are not eligible for compensation for your injury or complication under law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

7. Will I benefit from the study?

The study aims to further medical knowledge and may improve future treatment of cervical cancer, however it may not directly benefit you. Some studies have suggested that extra chemotherapy may increase the chance of cure whilst others have shown no advantage. We hope that by carrying out this study we will be able to confirm if extra chemotherapy treatment after standard chemo-radiation can increase the likelihood of cure of cervical cancer.

8. Will taking part in this study cost me anything?

There will be no costs to you during the study for medical services or laboratory tests that are required as part of the study and outside the standard of care for your disease. Any costs related to the standard of care treatment for your disease at your hospital will still apply. Taking part in this study may result in added costs to you such as transport. You will not be paid for participation in this study.

9. How will my confidentiality be protected?

Nursing and medical staff, including your general practitioner, involved in your care will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will not be disclosed without your permission, except as required by law.

Your health records and any information obtained during the study may be examined by authorised representatives of the hospital's Health Research Ethics Committee, the study sponsor (University of Sydney), the company providing paclitaxel (Hospira)

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or by regulatory authorities such as the Australian Government's Therapeutic Goods Administration (TGA) or as required by law, for the purposes of verifying the study procedures or data. By signing the Consent Form, you authorise access to this confidential information to the relevant study personnel and regulatory authorities as noted above.

10. What happens with the results?

Your doctor will inform you about your own results where relevant. The results of this study will be analysed after all participants have been followed up for 3 years. When this study is completed and the results have been analyzed, the results will be published and presented in peer reviewed journals, at national/international cancer conferences or at other professional forums. You will not be personally identified in any report or publication. Once the results are available you will be able to ask your doctor about these.

11. What happens to my treatment when the study is finished?

Once your treatment is completed you will continue to see your doctor on a regular basis. These appointments are scheduled every 3 months for the first 2 years, and every six months for a further 3 years. The total follow-up period will be 5 years. Any decision about further treatment will be made by your treating doctor in consultation with you.

12. Further Information or any problems

If you require further information or if you have any problems concerning this study (for example, any side effects), you can contact the principal investigator or study staff. The investigators responsible for this study are *[list the names and contact phone numbers, including after hours numbers]*.

Name: *[Site principal investigator or study team contact person]*

Position:

Telephone:

13. Who should I contact if I have concerns about the conduct of this study?

This study has been approved by *Cancer Institute NSW Clinical Research Ethics Committee*. If you have concerns or complaints about the conduct of this study, you should contact *[name]* who is the person nominated by the Human Research Ethics Committee to receive complaints from research participants. You should contact them on *[number]* and quote *[HREC project number]*.

Name: *[This person should be someone independent of the study]*

Position:

Telephone:

**Thank you for taking the time to consider being part of this study.
If you wish to take part in this study, please sign the attached consent form.**

This information sheet is for you to keep.



[Hospital letterhead]

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PARTICIPANT CONSENT FORM

I, [name]

Of..... [address]

have read and understood the Information for Participants on the above named research study. I understand that I am agreeing to participate in a research study.

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk, discomfort or side effect, and of their implications as far as they are currently known by the researchers.

I understand that the research project will be carried out according to the principles in the National Health & Medical Research Council Statement on Ethical Conduct in Research Involving Humans.

I freely choose to participate in this study and understand that I can withdraw at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME:.....

SIGNATURE:

DATE

NAME OF INVESTIGATOR:

SIGNATURE OF INVESTIGATOR:

DATE:

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PARTICIPANT INFORMATION AND CONSENT FORM

Translational Research

Study Title: A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone

THE OUTBACK TRIAL



Principal Investigator: [name of site principal investigator]

The sponsor for this study in Australia and New Zealand is the University of Sydney.

Hospira is providing one of the study drugs called paclitaxel for Australian sites. **This form is in addition to the consent form you signed for the OUTBACK main study.**

You are being asked to take part in this research project because you have consented to participate in the OUTBACK main study.

This Participant Information contains information about the additional blood and tissue component of this study. Its purpose is to explain to you as openly and clearly as possible all the procedures involved before you decide whether or not to take part in it.

Please read this Participant Information carefully. Feel free to ask questions about any information in the document. You may also wish to discuss the study with a relative or friend or your local health worker. Feel free to do this.

Once you understand what the study is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent form, you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of the Participant Information and Consent form to keep as a record.

1. What is the purpose of this study?

The purpose of the study is to collect blood and tissue samples for future laboratory testing. Research will be undertaken to determine ways to improve how we deliver therapy for cervical cancer and manage side effects, as well as how the disease arises in the first place. We will also try and determine why some patients might benefit from treatment more than others. This is what is referred to as 'Translational Research'.

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This may include testing to see if genetic reasons can be identified that explain why some patients may benefit more from the treatment being given in this study than others, such as genetic differences in the way that your body handles chemotherapy drugs or reacts to radiotherapy. All future research for which your samples will be used will relate to cervical cancer. Genetic testing for diseases that may run in families will not be performed on your samples.

2. What does the study involve?

We are requesting your consent to allow us to use, for research purposes, any tissue samples that may have been taken from you previously as a biopsy or during surgery. These tissue samples are routinely stored in pathology stores as required by law.

Additionally, one blood sample will be taken by a qualified practitioner at the beginning of the study (approximately 35 ml, which equals about 2 tablespoons). When you give blood, you may feel faint, or experience mild pain, bruising, irritation or redness at the site where the blood is taken from. In rare cases, you may get an infection. Some of this blood sample will be used to get a sample of your genetic material (DNA inherited from your mother and father).

If you require another biopsy for clinical reasons (such as confirmation of diagnosis) some additional fresh frozen tissue from that biopsy will be collected for planned laboratory studies. If you do not need another biopsy for clinical reasons, then you DO NOT require a repeat biopsy to participate in this study.

All samples (tissue/blood) will be stored at the hospital site for the duration of the study. At a future point in time the samples will be shipped to a central laboratory for testing.

You will not receive any payment for taking part in this translational research.

There will not be any anticipated expenses for you while taking part in this translational research.

The choice whether to participate or not is entirely up to you. Your ability to participate in the main study will not be affected in any way by your decision.

3. What will be done with my samples?

The samples will be coded with a number and will NOT be labeled with any information that directly identifies you. The connection between the code and your name will only be kept by your study doctor. Your samples will be given the same code as your other study information and kept in locked storage. Anyone who works with your samples will hold the information and results in confidence. Your samples may be kept for up to 15 years after the end of the study. Any samples remaining at that time will be destroyed.

Therefore, all current and future studies will only be conducted if they have achieved the approval of a Human Research Ethics Committee (HREC), which is comprised of clinical, scientific and community representatives and operates under national guidelines. In addition any studies will also require approval by the Australia New Zealand Gynaecological Oncology Group (ANZGOG).

Some research studies may involve sending your samples or de-identified health information interstate/overseas. If so, these researchers are required to demonstrate (to a local HREC) that they meet the appropriate Australian standards of ethics and privacy as detailed above before any samples or health information will be released.

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Whilst the aim of our research is to improve the health of our community, sometimes research may lead to findings that result in the development of a commercial test or treatment. Australian law indicates that there is no financial reward or payment to you in this event.

4. Protecting your privacy

We seek your consent to access medical information kept about you that is relevant to medical research, including information that may come from hospital case notes, GP records, past diagnoses or information held by the Department of Health.

Samples will be identified by a code only and it will not be possible for researchers using them to link this to your personal information themselves. We abide by all state and Federal Privacy legislation at all times.

It is important to note that there may be circumstances under Privacy legislation where disclosure of your health information kept by the study sponsor (University of Sydney) could be obtained, if requested, for example, as a result of a court order.

5. What will happen with the results?

Your doctor will inform you about your own results where relevant.

If you give us your permission by signing the Consent Form, we plan to discuss/publish the results. That involves:

- Writing up the study results for peer-reviewed journals
- Sharing the results with other academic research groups, universities, or companies, to better understand cervical cancer or to further develop anti-cancer drugs
- Using the results to plan new studies to learn more about cervical cancer or other conditions

In any publication, information will be provided in such a way that you cannot be identified.

Results of the study will be provided to you, if you wish, by your study doctor.

6. What are the potential risks?

If you allow us to use your tissue, these samples are not intended to be used in your diagnosis or treatment. Risks of blood samples being drawn include pain, bruising, bleeding, temporary redness of the skin at the injection site, infection and light-headedness. Care will be taken to avoid these difficulties.

7. What are the potential benefits?

It is unlikely that the research performed will be of direct benefit to you. The results may help us to better understand how to diagnose or treat patients with your type of cancer more effectively.

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8. What if I change my mind?

Your tissue will be stored until it is used up or you contact the ANZGOG to request its destruction. If you wish to have your sample withdrawn, or stop access to your health information, please notify your doctor in writing. A letter confirming removal of your sample and/or health information will be sent to you.

9. What happens to my tissue if I die?

In the event of your death, we will continue to store tissue and make it available to researchers. Your tissue will continue to be used in cervical cancer research subject to the conditions described in section 3.

10. Further Information or Any Problems

If you require further information or if you have any problems concerning this project, you can contact one of the researchers or the study coordinator. Contact numbers are:

Dr	(Principal Investigator)	Telephone:
Dr	(Investigator)	Telephone:
Dr	(Oncology Research Fellow)	Telephone:

After hours you can call the hospital switchboard on and ask for the oncology registrar on call.

The Clinical Trial Coordinator for this study isand he/she can be contacted on

11. Other Issues

If you wish to contact someone independent of the study about ethical issues or your rights, you may contact Chairperson of the..... Human Research Ethics Committee, Phone You will need to give the name of one of the researchers given in section 10 above.

12. Ethical Guidelines

This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (2007) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

Thank you for taking the time to consider being part of this study.

If you wish to take part in this study, please sign the attached consent form.

This information sheet is for you to keep.



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PARTICIPANT CONSENT FORM

I, [name]

of.....[address] have read and understood the

Information for Participants on the above named research study.

I understand that I am agreeing to participate in a research study.

I have been made aware of the procedures involved in the study, including any known or expected inconvenience, risk and of their implications as far as they are currently known by the researchers.

I understand that the research project will be carried out according to the principles in the National Health & Medical Research Council Statement on Ethical Conduct in Research Involving Humans.

I freely choose to donate:

(please tick box(es) below)

- my tissue (from previous biopsy, and future biopsy if clinically indicated)
- my blood (35ml blood sample)

and understand that I can withdraw my tissue or blood at any time.

I also understand that the research study is strictly confidential.

I hereby agree to participate in this research study.

NAME:

SIGNATURE:

DATE:

NAME OF WITNESS:


SIGNATURE OF WITNESS:

NAME OF INVESTIGATOR:

SIGNATURE OF INVESTIGATOR:

The OUTBACK Trial

Appendix 2. Quality of Life (QOL) forms

 40393	OUTBACK (ANZGOG 0902)	Study No. <input type="text"/> <input type="text"/> <input type="text"/> / <input type="text"/> <input type="text"/> <input type="text"/> Visit No.
Site number <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	Example: Study No. 001 = 001, Study No. 002 = 002	Enter Visit No. as per the box marked on the cover page, e.g. Baseline = 001, Adj cycle 1 = 101, Adj cycle 2 = 102, etc

A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: THE OUTBACK TRIAL

Patient Quality of Life Booklet

This booklet has 10 pages

Initials (first, middle, last, e.g. XXX or X-X)

Date of birth / /
(DD / MM / YYYY)

Today's date (date completed) / /
(DD / MM / YYYY)

Please cross the box corresponding to the time point this booklet is being completed.
Please enter the corresponding visit number in the header of this booklet.

- | | |
|--|--|
| <input type="checkbox"/> Baseline (Visit No. 001) | <input type="checkbox"/> Follow-up 6 months (Visit No. 301) |
| <input type="checkbox"/> Adj chemo cycle 1 (Visit No. 101) | <input type="checkbox"/> Follow-up 9 months (Visit No. 302) |
| <input type="checkbox"/> Adj chemo cycle 2 (Visit No. 102) | <input type="checkbox"/> Follow-up 12 months (Visit No. 303) |
| <input type="checkbox"/> Adj chemo cycle 3 (Visit No. 103) | <input type="checkbox"/> Follow-up 15 months (Visit No. 304) |
| <input type="checkbox"/> Adj chemo cycle 4 (Visit No. 104) | <input type="checkbox"/> Follow-up 18 months (Visit No. 305) |
| <input type="checkbox"/> End of treatment (Visit No. 200) | <input type="checkbox"/> Follow-up 21 months (Visit No. 306) |
| | <input type="checkbox"/> Follow-up 24 months (Visit No. 307) |
| | <input type="checkbox"/> Follow-up 30 months (Visit No. 308) |
| | <input type="checkbox"/> Follow-up 36 months (Visit No. 309) |



The OUTBACK Trial



OUTBACK (ANZGOG 0902)

Study No.

 /

Visit No.

Example:
Study No. 001 = 001,
Study No. 002 = 002

Enter Visit No. as per the box
marked on the cover page,
e.g. Baseline = 001,
Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?		2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the past week:				
	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4



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OUTBACK (ANZGOG 0902)

Study No. / Visit No.

Example:
Study No. 001 = 001,
Study No. 002 = 002

Enter Visit No. as per the box marked on the cover page,
e.g. Baseline = 001,
Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor Excellent



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Study No. / Visit No.

Example:
Study No. 001 = 001,
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Enter Visit No. as per the box
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EORTC QLQ-CX24

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems, please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had cramps in your abdomen?	1	2	3	4
32. Have you had difficulty in controlling your bowels?	1	2	3	4
33. Have you had blood in your stools (motions)?	1	2	3	4
34. Did you pass water/urine frequently?	1	2	3	4
35. Have you had pain or a burning feeling when passing water/urinating?	1	2	3	4
36. Have you had leaking of urine?	1	2	3	4
37. Have you had difficulty emptying your bladder?	1	2	3	4
38. Have you had swelling in one or both legs?	1	2	3	4
39. Have you had pain in your lower back?	1	2	3	4
40. Have you had tingling or numbness in your hands or feet?	1	2	3	4
41. Have you had irritation or soreness in your vagina or vulva?	1	2	3	4
42. Have you had discharge from your vagina?	1	2	3	4
43. Have you had abnormal bleeding from your vagina?	1	2	3	4
44. Have you had hot flushes and/or sweats?	1	2	3	4
45. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
46. Have you felt less feminine as a result of your disease or treatment?	1	2	3	4
47. Have you felt dissatisfied with your body?	1	2	3	4



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Study No.

Visit No.

Example:
Study No. 001 = 001,
Study No. 002 = 002

Enter Visit No. as per the box
marked on the cover page,
e.g. Baseline = 001,
Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

During the past 4 weeks:

	Not at all	A little	Quite a bit	Very much
48. Have you worried that sex would be painful?	1	2	3	4
49. Have you been sexually active?	1	2	3	4

Answer these questions only if you have been sexually active during the past 4 weeks:

	Not at all	A little	Quite a bit	Very much
50. Has your vagina felt dry during sexual activity?	1	2	3	4
51. Has your vagina felt short?	1	2	3	4
52. Has your vagina felt tight?	1	2	3	4
53. Have you had pain during sexual intercourse or other sexual activity?	1	2	3	4
54. Was sexual activity enjoyable for you?	1	2	3	4

Example only - do not use for data collection



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Study No. / Visit No.

Example:
Study No. 001 = 001,
Study No. 002 = 002

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e.g. Baseline = 001,
Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

EORTC QLQ-OV28 (selected questions)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost hair?	1	2	3	4
39. <u>Answer this question only if you had hair loss:</u> Were you upset by the loss of your hair?	1	2	3	4
40. Did food and drink taste different from usual?	1	2	3	4
43. Have you felt weak in your arms or legs?	1	2	3	4
44. Did you have aches or pains in your muscles or joints?	1	2	3	4
45. Did you have problems with hearing?	1	2	3	4
47. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4



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Study No. / Visit No.

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marked on the cover page,
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Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

EORTC QLQ-PR25 (selected questions)

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
39. Have your daily activities been limited by your urinary problems?	1		3	4
40. Have your daily activities been limited by your bowel problems?		2	3	4

FACT/GOG-NTX-4 (Version 4)

Below is a list of statements that other people with your illness have said are important.

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some what	Quite a bit	Very much
NTX1	I have numbness or tingling in my hands	0	1	2	3	4
NTX2	I have numbness or tingling in my feet	0	1	2	3	4
NTX3	I feel discomfort in my hands	0	1	2	3	4
NTX4	I feel discomfort in my feet	0	1	2	3	4



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Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

SVQ (Extended version)

SEXUAL FUNCTION-VAGINAL CHANGES QUESTIONNAIRE

Physical contact and sexual relations can be an important part of many people's lives. People who suffer from illnesses involving their pelvic region may experience changes in their sex life.

The questions below refer to this. The information you provide will remain strictly confidential. Please answer all the questions yourself by circling the number that best applies to you.

Some of the questions may not apply to women who have same sex relationships.

Part 1

During the past month:	Not at all	A little	Quite a bit	Very much	
1. Have you been interested in close physical contact (a kiss and a cuddle)?	1	2	3	4	
2. Have you had close physical contact with your family and close friends?	1	2	3	4	
3. Have you had any interest in sexual relations?		2	3	4	
Yes No					
4. Do you have a partner? (If not, please continue to question 8)	1	2			
Not at all A little Quite a bit Very much					
5. Has your partner wanted to have sexual relations?	1	2	3	4	
No Yes, 1-2 times a month Yes, 3-4 times a month Yes, 1-2 times a week Yes, more than twice a week					
6. Have you had sexual relations? (If you have answered no to this question, please continue to question 8)	1	2	3	4	5
Not at all A little Quite a bit Very much					
7. Did your partner have difficulty achieving an erection?	1	2	3	4	
8. Has your sex life/lack of sex life made you worry?	1	2	3	4	



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OUTBACK (ANZGOG 0902)

Study No.

 /

Visit No.

Example:
Study No. 001 = 001,
Study No. 002 = 002

Enter Visit No. as per the box
marked on the cover page,
e.g. Baseline = 001,
Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

For the following questions please circle the number between 1 and 7 that best applies to you.

During the past month:

9. How satisfied or dissatisfied have you been with your sex life/lack of sex life?
- | | | | | | | |
|----------------------|---|---|---|---|---|-------------------|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| Very
dissatisfied | | | | | | Very
satisfied |
10. How satisfied or dissatisfied have you been with your appearance?
- | | | | | | |
|----------------------|---|---|---|---|-------------------|
| 1 | 2 | 3 | 4 | 5 | 7 |
| Very
dissatisfied | | | | | Very
satisfied |

Please go on to part 2 if you have been sexually active during the past month.
If you not been sexually active during the past month, please go on to part 3.

The following questions apply to you only if you have been sexually active during the past month.
Please answer all the questions yourself by circling the number that best applies to you.

Part 2

During the past month:

- | | Not at
all | A little | Quite a
bit | Very
much |
|--|---------------|----------|----------------|--------------|
| 11. Did you feel that your vagina was dry during intercourse? | 1 | 2 | 3 | 4 |
| 11a. If yes, has it bothered you? | 1 | 2 | 3 | 4 |
| 12. Have you had any pain during intercourse? | 1 | 2 | 3 | 4 |
| 12a. If yes, has it bothered you? | 1 | 2 | 3 | 4 |
| 13. Have you experienced bleeding during intercourse? | 1 | 2 | 3 | 4 |
| 13a. If yes, has it bothered you? | 1 | 2 | 3 | 4 |
| 14. Did you feel that intercourse was bothersome because your vagina felt too small? | 1 | 2 | 3 | 4 |

- | | Never | Occasion
ally | Often | Always |
|---|-------|------------------|-------|--------|
| 15. Were you able to complete sexual intercourse? | 1 | 2 | 3 | 4 |
| 16. Have you reached orgasm? | 1 | 2 | 3 | 4 |

- | | Not at
all | A little | Quite a
bit | Very
much |
|--|---------------|----------|----------------|--------------|
| 17. Did you feel relaxed after having sex? | 1 | 2 | 3 | 4 |

SVQ (Extended version)
English

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Study No.

 /

Visit No.

Example:
Study No. 001 = 001,
Study No. 002 = 002

Enter Visit No. as per the box
marked on the cover page,
e.g. Baseline = 001,
Adj cycle 1 = 101,
Adj cycle 2 = 102, etc

The following questions are about your experience of any changes in your feelings and/or your sex life today compared to before you were diagnosed with cancer.

Please answer all the questions yourself by circling the number that best applies to you.

Part 3	I am <i>less</i> interested now	It is unchanged	I am <i>more</i> interested now
CH1. Has your interest in close physical contact changed since you were diagnosed with cancer?	1	2	3
CH2. How much close physical contact do you have with your family and close friends compared to before you were diagnosed with cancer?	I have <i>less</i> than before	It is unchanged	I have <i>more</i> than before
	1	2	3
CH3. Has your interest in sexual relations changed since you were diagnosed with cancer?	I am <i>less</i> interested now	It is unchanged	I am <i>more</i> interested now
	1	2	3
The following question applies to you only if you have a partner:	He is <i>less</i> interested now	It is unchanged	He is <i>more</i> interested now
CH4. Has your partner's interest in sexual relations changed since you were diagnosed with cancer?	1	2	3
The following question applies to you only if you are sexually active:	It is <i>less</i> dry now	It is unchanged	It is <i>drier</i> now
CH5. Has the dryness of your vagina changed since you were diagnosed with cancer?	1	2	3
CH6. Do you feel that the size of your vagina has changed since you were diagnosed with cancer?	It is <i>smaller</i> now	It is unchanged	It is <i>larger</i> now
	1	2	3
The following question applies to you only if you have experienced any pain during intercourse:	I have <i>less</i> pain now	It is unchanged	I have <i>more</i> pain now
CH7. Has the pain you experience during intercourse changed since you were diagnosed with cancer?	1	2	3

SVQ (Extended version)
English

Thank you for your help

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Appendix 3. Definition of Corpus Positive disease on MRI

A tumour is said to be corpus invasive if the tumour is seen to infiltrate beyond the cervico-uterine plane into the isthmus and beyond. The junction of uterus and cervix is best observed in the MR images taken in the sagittal plane. The cervico-uterine junction is located where internal cervical os continues with the uterine cavity. In a patient whose entire cervix is distorted by the presence of cervix cancer, the cervico-uterine junction is identified where the proximal outer contour of the cervix abruptly widens to merge with the corpus.

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Appendix 4. RECIST 1.1 Criteria

Response Evaluation Criteria in Solid Tumours (RECIST v1.1)

These instructions are based on the guidelines recommended in Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). (Eur J Cancer 2009; 45: 228-47)

1. Evaluable for response.

All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

2. Disease and lesion definitions

2.1 Measurable Disease. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

2.2 Non-measurable Disease. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

2.3 Target Lesions. When more than one measurable tumour lesion is present at baseline all lesions up to a *maximum of 5 lesions in total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological lymph nodes must meet the criterion of having a short axis of ≥ 15 mm by CT scan and only the *short* axis of these lymph nodes will contribute to the baseline sum. All other pathological lymph nodes (those with a short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of target lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

2.4 Non-target Lesions. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-*

The OUTBACK Trial

target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

3. Response Definitions

All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of any specified tumour markers (no tumour markers for this trial). Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol.

Partial Response (PR): at least a 30% decrease in the sum of measures for target lesions (longest diameter for tumour lesions and short axis measure for target lymph nodes), taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table 1: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
<i>Target lesions ± non target lesions</i>				
CR	CR	No	CR	Normalization of specified tumour markers, AND lymph nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once \geq 4 wks. from baseline [note, protocol may define; 6-8 weeks is recommended]
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	

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Any	PD	Any	PD	
Any	Any	Yes	PD	
<i>Non target lesions ONLY</i>				
No Target	CR	No	CR	Normalization of specified tumour markers AND lymph nodes < 10mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
<p>Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>”. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.</p>				

4. Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

5. Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomisation for randomized studies) until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

6. Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent, unless the protocol specifies otherwise. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

- 6.1 Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and $\geq 10\text{mm}$ as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.
- 6.2 Chest X-ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
- 6.3 CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less.

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When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

- 6.4 Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.
- 6.5 Endoscopy, Laparoscopy. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
- 6.6 Tumour Markers. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. There are no specified tumour markers for this trial.
- 6.7 Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

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Appendix 5. FIGO 2008 staging for carcinoma of the cervix uteri

Carcinoma of the cervix uteri.

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤ 5 mm and largest extension ≥ 7 mm
IA1	Measured stromal invasion of ≤ 3.0 mm in depth and extension of ≤ 7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA *
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney **
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

*All macroscopically visible lesions—even with superficial invasion—are allotted to stage IB carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.00 mm and a horizontal extension of not >7.00 mm. Depth of invasion should not be >5.00 mm taken from the base of the epithelium of the original tissue—superficial or glandular. The depth of invasion should always be reported in mm, even in those cases with “early (minimal) stromal invasion” (~ 1 mm).

The involvement of vascular/lymphatic spaces should not change the stage allotment.

**On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. All cases with hydronephrosis or non-functioning kidney are included, unless they are known to be due to another cause.

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Appendix 6. Information requirements for PET reports

The following information is required to complete the PET-related case report forms:

- Blood glucose level prior to PET scan
- Uptake time
- Method of scan (PET/CT or PET only)
- Liver SUV average
- Cervix SUV max
- Nodes involved (location, number of nodes, SUV max)