The OUTBACK Trial

A Phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone (ANZGOG 0902/GOG-0274/RTOG 1174)

STUDY HANDBOOK

Please read in conjunction with the current version of the OUTBACK protocol

GOG and RTOG Legacy Group Edition
Version 3.0, July 7, 2014
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1.0 STUDY COORDINATION

The OUTBACK Trial is an independent investigator-initiated study conducted under the auspices of ANZGOG as a multicentre study.

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

This study is being carried out in the United States under the sponsorship of the Gynecologic Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG) legacy groups. The GOG and RTOG are funded by the Federal Government through the National Cancer Institute (NCI).

The clinical components of the trial including participation from member institutions from the GOG and RTOG legacy groups will be managed and coordinated by ANZGOG. Specimen banking and translational research from GOG member institutions will be managed and coordinated by the GOG legacy group and specifically the GOG Committee on Experimental Medicine and the GOG Cervix and Vulvar Committee.

RTOG legacy will manage and coordinate its own specimen banking and translational research associated with this study.

The Principal Investigator (05/13/2013)

The study chair is A/Prof Linda Mileshkin at Peter MacCallum Cancer Centre, Melbourne, Australia.

The study chair will be responsible for clarifying protocol-specific and associated medical questions arising at Australian and New Zealand sites, and for overseeing satisfactory trial conduct internationally.

The lead radiation oncologist is A/Prof Kailash Narayan and the Lead in Quality of Life is Prof Madeleine King.

Dr. Kathleen Moore at University of Oklahoma Health Science Center will be responsible for clarifying protocol-specific and associated medical questions arising at GOG institutions. Her contact information is as follows:

University of Oklahoma Health Science Center
920 S. L. Young Blvd.
WP 2410
Oklahoma City, OK 73104
Phone: (405) 271-8707 Fax: (405) 271-2976
Email: Kathleen-moore@ouhsc.edu
Dr. William Small at Loyola University Medical Center will be responsible for clarifying protocol-specific and associated medical questions arising at RTOG institutions. His contact information is as follows:

Professor and Chair
Loyola University Medical Center
Department of Radiation Oncology
2160 S 1st Ave
Maguire Center, Rm 2932
Maywood, IL 60153
Phone: (708) 216-2559 Fax: (708) 216-6076
Email: wmsmall@lumc.edu (07/29/13 updated)

The Coordinating Centre (05/13/2013)
The NHMRC Clinical Trials Centre (CTC) is the coordinating data centre for this trial, responsible for handling investigator authorisation procedures, coordinating submission of regulatory documents, overall data management, and it serves as a back-up for the randomisation of patients.

The NHMRC CTC is responsible for all administrative procedures required for the trial following standard operating procedures and applicable regulatory requirements.

In the United States, the Cancer Therapy Evaluation Program (CTEP), Clinical Investigations Branch (CIB) will provide scientific coordination and oversight of this cooperative group trial as well as assist with the collaboration and implementation of this international clinical trial.

Contact Details
Mailing Address: The OUTBACK Trial
(Snail mail) NHMRC Clinical Trials Centre
Locked Bag 77
Camperdown NSW 1450
Australia

Courier Address:
Street address must be used. Couriers cannot deliver to the Locked Bag address.

The OUTBACK Trial
NHMRC Clinical Trials Centre
Level 6, Lifehouse Building
119-143 Missenden Rd
Camperdown NSW 2050
Australia

Phone: +61-2-9562-5000
Fax: +61-2-9562-5094
Email: outback@ctc.usyd.edu.au
1.1 Trial organisation

The NHMRC CTC is the coordinating data centre for this Intergroup Trial being led by ANZGOG, and is responsible for the overall trial conduct (including protocol finalisation, trial activation, data management, statistical analysis and publication).

For GOG and RTOG legacy sites participating in this trial, randomization for patients will occur through the ANZGOG coordinating center (InForm system) while the legacy groups GOG and RTOG will manage tissue banking for this trial as will be discussed below.

1.2 Investigator authorisation procedure (05/13/2013)

Investigators will be authorized to randomize patients in this trial only when the GCIG coordinating office has notified the NHMTC CTC that all ethical and regulatory approvals and pre-study essential documents are in place via the site approval form. Upon receipt of this form, and completion of the InForm training exercise, authorized investigators and site staff will be given access to the live OUTBACK database.

US Sites must submit all IRB approvals (initial and continuing) as well as the approved informed consent to the CTSU Regulatory Office, at the Coalition of Cancer Cooperative Groups in Philadelphia. A CTSU IRB/Regulatory Approval Transmittal Sheet should be submitted along with the CTSU IRB Certification Form or its equivalent. (CTSU forms can be downloaded at https://www.ctsu.org/public/rss2_page.aspx). IRB submissions can be faxed or emailed (preferred methods) or mailed to:

Cancer Trials Support Unit (CTSU)
ATTN: Coalition of Cancer Cooperative Groups (CCCG)
Suite1100
1818 Market Street
Philadelphia, PA 19103
FAX: 1-215-569-0206
2.0 RECRUITMENT (05/13/2013)

2.1 Screening
Participating centres are requested to fill in screening logs for all patients eligible for the study. Note: Screening logs are recommended but optional.

2.2 Consent
The GOG and RTOG patient informed consent must be signed by all participants prior to carrying out any procedures or interventions.

The General Information About the Collection and Use of Specimens for the Research Portion of the consent must be signed by all study participants consenting to donating tissue and blood samples.

Participants may decline participation in the Translational Component and still take part in the Main Study.
3.0 RANDOMISATION (05/13/2013)

Patient randomisation will only be accepted from authorised investigators. A web-based randomisation system, built and maintained by the NHMRC CTC, is being used. Sites are given logins and passwords in order to perform their own randomisations.

The NHMRC CTC will act as a back-up for performing randomisations, in case a site is temporarily unable to access the database and if the randomisation is urgent.

At the end of the randomisation procedure, the sequential participant identification number and the treatment will be allocated.

NOTE: If at any time you are experiencing difficulty accessing the OUTBACK database please email the study mailbox at outback@ctc.usyd.edu.au.

3.1 Step-by-step guide for randomising a patient

The website address for the OUTBACK database is emailed to sites at the time of activation.

Each trial staff will be set up with their own login details.

This is the login page

How to log in:
Enter your user name and password.
Click ‘Log in’.  
Please remember that the login fields are case sensitive.

After logging in, you will see the trial homepage.  
There are links to the current protocol and CTC AE v4, as well as the contact details of the study team.
To start randomising a patient, click on 'Enroll', on the left of the screen.

You will see this page. Click ‘Add candidate’ at the bottom right of the screen.
You will see this page.
Enter the patient’s data in the fields provided.
Once all the information is entered, click ‘Submit’ at the bottom right of the screen.
If there are any issues with the data entered on the previous screen, you will see comments in the ‘Screening Failure’ column, **in the row that corresponds to the patient that you have entered**.

To address those comments, click on the patient’s screening number in the first column, which will take you back to the previous screen. All required information needs to be entered before you can progress with the randomisation.

If there are no issues with the data entered on the previous screen, you can proceed with the randomisation.

To continue, click on ‘Enrol’ in the last column of the row that corresponds to the patient that you have entered.

You will see this page.

Enter the clinician who has confirmed eligibility for the patient.

Please remember that this clinician needs to be a study clinician.

Click on ‘Submit’ at the bottom right of the screen.
You will see this page.
Click on ‘Enrol’ at the bottom right of the screen.
You will see this page.
The information displayed is for internal use only.
Click on 'Go to first visit' at the bottom right of the screen.

<table>
<thead>
<tr>
<th>Visit</th>
<th>Initiation Date</th>
<th>Scheduled Date and Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1 (RAPPO)</td>
<td>Sunday, January 09, 2011</td>
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<tr>
<td>Visit 2 (AABL, INI)</td>
<td>Sunday, February 06, 2011</td>
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<tr>
<td>Visit 3 (NODAL ASSESS (RL))</td>
<td>Sunday, February 06, 2011</td>
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<tr>
<td>Visit 4 (PERF (RL))</td>
<td>Sunday, February 06, 2011</td>
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<td>Visit 5 (RECIST)</td>
<td>Unscheduled Visit(0)</td>
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<tr>
<td>Visit 6 (CRL_C1)</td>
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<td>Visit 7 (Ch_C2)</td>
<td>Sunday, February 27, 2011</td>
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<td>Visit 8 (CRL_C3)</td>
<td>Sunday, March 06, 2011</td>
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<td>Visit 9 (CRL_C4)</td>
<td>Sunday, March 13, 2011</td>
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<td>Sunday, March 20, 2011</td>
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<td>Visit 11 (MARIO)</td>
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<tr>
<td>Visit 12 (TeoFLUP)</td>
<td>Unscheduled Visit(0)</td>
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<tr>
<td>Visit 13 (GOT)</td>
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<td>Visit 14 (IPF)</td>
<td>Dynamically Scheduled Visit</td>
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<td>Visit 15 (NODAL ASSESS)</td>
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<td>Visit 16 (AOI_C1)</td>
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<td>Visit 17 (AOI_C2)</td>
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<td>Visit 19 (AOI_C4)</td>
<td>Dynamically Scheduled Visit</td>
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<td>Visit 20 (GOT)</td>
<td>Dynamically Scheduled Visit</td>
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<tr>
<td>Visit 21 (IPF)</td>
<td>Dynamically Scheduled Visit</td>
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<td>Visit 22 (NODAL ASSESS)</td>
<td>Dynamically Scheduled Visit</td>
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<tr>
<td>Visit 23 (IDON)</td>
<td>Dynamically Scheduled Visit</td>
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</table>

You will see this page.
Enter the current date and click ‘Submit’ at the bottom right of the form.
This will transfer all data previously entered on the screening form. Review the data to make sure everything is correct.

A new tab has appeared at the top. Click on the new tab labelled ‘Rand Details’.

You will see this page. Answer Item 4: Ready for randomisation ‘Yes’ Click ‘Submit’ at the bottom right of the screen.
You will see this page.
This is your randomisation confirmation.
Print this page and file it in the patient's notes.
To print, go to the 'Select Action' field at the bottom of the screen and select 'Print Preview', then click 'Apply'. This will open the print screen.

Click 'Print' at the bottom right of the screen.
After printing, click ‘Return’ at the bottom right of the screen to return to the ‘Rand Details’ screen.

Congratulations! You have successfully randomised a patient to the OUTBACK trial.

Click ‘Return’ at the bottom right of the screen to return to the Time and Events Schedule, if you want to continue to enter data.
Alternatively, click ‘Logout’ on the top left of the screen if you want to log out of the database.

**GOG Registration (05/13/2013)**

After the patient has been registered in the NHMRC CTC registration system, the institution **must** register the patient with the GOG using the web-based registration application or by phone if necessary (800-523-2917). This will ensure per capita payment and allow you to obtain a Tissue Bank ID. Instructions for web-based registration and randomization can be found by going to the GOG Web Menu page, selecting "Start/finish a patient registration," and then selecting "Directions" found on the left side of the page.

**RTOG Registration (05/13/2013)**

RTOG sites will be required to re-register the patient for administrative and re-imbursement updates via the RTOG website. Please have the ANGOG patient number assigned by the ANZGOG InForm™ system readily available before attempting to re-register the patient via the RTOG registration portal. Once you sign on to the RTOG data-login system using your RTOG username and password, choose your institution number, scroll to the bottom of the page and click “Continue to Main Menu,” select patient registration, and then type 1174 in the study number box.

**NOTE:** RTOG non-US member institutions will need to contact RTOG Regulatory, as study participation to this trial is limited.
4.0 CHEMORADIATION

4.1 Radiotherapy
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.

Brachytherapy dose and fractionation schemes should be designed so that the total dose to Point A is between 80 – 86.4 Gy (for centres using HDR this is EQD2 using $\alpha/\beta_{10}$).

Three to five fractions of HDR brachytherapy are permitted.

Examples of dose and fractionation schemes are given in the protocol in 8.3.2.2.

BT dose prescription
Brachytherapy dose can be prescribed to Manchester system Point A.

Point A:

- 2.0 cm sup to flange
- 2.0 cm lateral to tandem along line of tandem

Brachytherapy dose can be prescribed to individual target volumes, based on MRI, CT or US imaging.

An example of individual target is the ‘Peter MacCallum’ target volume.
Brachytherapy doses can be prescribed to volumes described by Gec-ESTRO recommendations.
Based on MRI imaging

- The target volume includes:
  - The whole cervix
  - Residual disease
  - Clinical disease
  - Infiltrative disease
  - Respect organ boundaries

Normal tissue doses (organs at risk) will be reported using ICRU report 38 methodology

ICRU 38 Bladder and Rectal points on lateral x-ray

Vaginal mucosa point

Vaginal mucosa point: surface of ovoid at mid source position

ICRU 38 Bladder point

ICRU 38 Rectal point
- ICRU 38 Bladder point:
  - A foley catheter is used
  - Fill balloon with 7 cm³ contrast
  - Pull catheter downwards to bring balloon against the urethra
  - On lateral xray or sagittal CT, MRI or US, draw antero-posterior line through centre of balloon
  - Reference point is on this line at posterior surface of balloon

ICRU 38 Rectal point:
- On lateral x-ray or sagittal CT, MRI or US antero-posterior line is drawn from the lower end of the intrauterine source (or from middle of the intravaginal sources)
- The point is located on this line 5 mm behind the posterior vaginal wall

Vaginal mucosa dose point: surface of ovoid at mid source position
Documentation requirements for Brachytherapy

- CTs, MRIs or US with applicator in-situ (preferred)
- Simulator films and DRR’s also accepted

- ICRU 38 Bladder & Rectal point on sagittal US

Treatment plan with source activities, dwell times, dwell positions and iso-plots.
Examples of images with applicator in-situ:
Please include magnification on images

**Total dose reporting (05/13/2013)**

Doses shall be reported as physical dose delivered by each modality to the central structures.

Please note that the CRF does not request the prescription doses to be recorded. The only doses required for reporting are the doses received at the central structures.

All centres must report the dose received at Point A.

Centres using image guided brachytherapy and prescribing to individual target volumes or Gec-ESTRO HR-CTV can choose to report the D90 HR-CTV in addition to reporting the dose at Point A. *(Recommendations from Gynecological (GYN) GEC-ESTRO Working Group* *(I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV Christine Haie-Meder, Richard Potter, Erik Van Limberg, Edith Briot Radiotherapy and Oncology (2005), 74:235–245.)*

Centres using HDR brachytherapy must also report total doses in EQD2.

This paper describes a simple Excel spreadsheet program that has been developed to assist clinicians to easily calculate equivalent doses to be used in HDR brachytherapy regimens. Equivalent doses are expressed as if given at 2 Gy per fraction (EQD2). The spreadsheet is available from the OUTBACK study team (outback@ctc.usyd.edu.au) (with permission from Dr S Nag).
Examples below show how the CRF will look when filled in (depending on how centres plan and prescribe treatment, central structures may receive different doses at each insertion. These need to be physically added together before filling in the CRF):

### Example 1: EBRT + LDR BT

**EBRT:** 45.00 Gy in 25 fractions (no nodal or parametrial boost given)

**LDR:** 2 x 20.00 Gy received at **Point A**

- **First insertion:** ICRU 38 Bladder = 14 Gy, ICRU 38 Rectum = 12 Gy, Vaginal Mucosa = 35 Gy
- **Second insertion:** ICRU 38 Bladder = 15 Gy, ICRU 38 Rectum = 13 Gy, Vaginal Mucosa = 40 Gy

<table>
<thead>
<tr>
<th><strong>Point A (right)</strong></th>
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<tbody>
<tr>
<td>2. * EBRT (physical dose)</td>
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<tr>
<td>3. * Nodal and/or parametrial boosts (physical dose)</td>
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<tr>
<td>4. * Brachytherapy (physical dose)</td>
</tr>
<tr>
<td>5. * Total physical dose (EBRT + Boosts + Brachy)</td>
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<tr>
<td>6. * Total biological dose for HDR (EQD2)</td>
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<th><strong>Point A (left)</strong></th>
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<tr>
<td>7. * EBRT (physical dose)</td>
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<tr>
<td>8. * Nodal and/or parametrial boosts (physical dose)</td>
</tr>
<tr>
<td>9. * Brachytherapy (physical dose)</td>
</tr>
<tr>
<td>10. * Total physical dose (EBRT + Boosts + Brachy)</td>
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<tr>
<td>11. * Total biological dose for HDR (EQD2)</td>
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<th><strong>HR-CTV (D90)</strong></th>
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<tr>
<td>12. * EBRT (physical dose)</td>
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<td>13. * Nodal and/or parametrial boosts (physical dose)</td>
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<tr>
<td>14. * Brachytherapy (physical dose)</td>
</tr>
<tr>
<td>15. * Total physical dose (EBRT + Boosts + Brachy)</td>
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<tr>
<td>16. * Total biological dose for HDR (EQD2)</td>
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<tr>
<th><strong>ICRU 38 Rectal Reference Point</strong></th>
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<tr>
<td>17. * EBRT (physical dose)</td>
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<td>18. * Nodal and/or parametrial boosts (physical dose)</td>
</tr>
<tr>
<td>19. * Brachytherapy (physical dose)</td>
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<tr>
<td>20. * Total physical dose (EBRT + Boosts + Brachy)</td>
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</table>
21. Total biological dose for HDR (EQD2)

**ICRU 38 Bladder Reference Point**

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<tbody>
<tr>
<td>22.</td>
<td>EBRT (physical dose)</td>
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<tr>
<td>23.</td>
<td>Nodal and/or parametrial boosts (physical dose)</td>
</tr>
<tr>
<td>24.</td>
<td>Brachytherapy (physical dose)</td>
</tr>
<tr>
<td>25.</td>
<td>Total physical dose (EBRT + Boosts + Brachy)</td>
</tr>
<tr>
<td>26.</td>
<td>Total biological dose for HDR (EQD2)</td>
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</tbody>
</table>

**Vaginal Mucosa**

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<tbody>
<tr>
<td>27.</td>
<td>EBRT (physical dose)</td>
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<tr>
<td>28.</td>
<td>Nodal and/or parametrial boosts (physical dose)</td>
</tr>
<tr>
<td>29.</td>
<td>Brachytherapy (physical dose)</td>
</tr>
<tr>
<td>30.</td>
<td>Total physical dose (EBRT + Boosts + Brachy)</td>
</tr>
<tr>
<td>31.</td>
<td>Total biological dose for HDR (EQD2)</td>
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</tbody>
</table>

Mandatory for all sites to report Point A dose

It is optional for sites using image guided brachytherapy to report HR-CTV D90

For PDR – depending on the type of PDR, dose will be reported in either physical or biological dose at the discretion of the individual centre.

Sites using HDR BT and reporting dose in EQD2 should use:

- $\alpha/\beta = 10$ Gy for Point A and HR-CTV
- $\alpha/\beta = 3$ Gy for Rectal, Bladder and Vaginal Mucosa points
**Example 2**  
**EBRT + HDR BT**

EBRT: 45.00 Gy in 25 fractions  (no parametrial or nodal boost given)  
HDR: 4 x 7.00 Gy prescribed to **individual target volume**  
Point A dose for each insertion was: 6.3 Gy (90% of 7.00 Gy) 4 x 6.3 = 25.2 Gy  
ICRU 38 Rectal dose for each insertion was 4.40 Gy 4 x 4.4 = 17.6 Gy  
ICRU 38 Bladder dose for each insertion was 3.9 Gy 4 x 3.9 = 15.6 Gy  
Vaginal mucosa dose for each insertion was 8.1 Gy 4 x 8.1 = 32.4 Gy

<table>
<thead>
<tr>
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<td>2.* EBRT (physical dose)</td>
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<td>3.* Nodal and/or parametrial boosts (physical dose)</td>
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<tr>
<td>4.* Brachytherapy (physical dose)</td>
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<tr>
<td>5.* Total physical dose (EBRT + Boosts + Brachy)</td>
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<td>6.* Total biological dose for HDR (EQD2)</td>
<td>78.8</td>
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<td>7.* EBRT (physical dose)</td>
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<tr>
<td>11.* Total biological dose for HDR (EQD2)</td>
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<th>HR-CTV (D90)</th>
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<td>12.* EBRT (physical dose)</td>
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<tr>
<td>16.* Total biological dose for HDR (EQD2)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>ICRU 38 Rectal Reference Point</th>
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</tr>
</thead>
<tbody>
<tr>
<td>17.* EBRT (physical dose)</td>
<td>45</td>
</tr>
<tr>
<td>18.* Nodal and/or parametrial boosts (physical dose)</td>
<td></td>
</tr>
<tr>
<td>19.* Brachytherapy (physical dose)</td>
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<tr>
<td>20.* Total physical dose (EBRT + Boosts + Brachy)</td>
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<tr>
<td>21.* Total biological dose for HDR (EQD2)</td>
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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>22.* EBRT (physical dose)</td>
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<td>23.* Nodal and/or parametrial boosts (physical dose)</td>
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</tr>
<tr>
<td>24.* Brachytherapy (physical dose)</td>
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</tr>
</tbody>
</table>
Mandatory for all sites to report Point A dose

It is optional for sites using image guided brachytherapy to report HR-CTV D90

For PDR – depending on the type of PDR, dose will be reported in either physical or biological dose at the discretion of the individual centre.
Sites using HDR BT and reporting dose in EQD2 should use:
α/β = 10 Gy for Point A and HR-CTV
α/β = 3 Gy for Rectal, Bladder and Vaginal Mucosa points
### Example 3
**EBRT + HDT BT**

EBRT: 45.00 Gy in 25 fractions (no parametrial or nodal boost given)

HDR: 4 x 7.00 Gy prescribed to **HR-CTV**

Point A dose for each insertion was 6.65 Gy (95% of 7.00 Gy)

4 x 6.65 = 26.6 Gy

D90 HR-CTV for each insertion was 6.09 Gy (87% of 7.00 Gy)

4 x 6.09 = 24.36 Gy

ICRU 38 Rectal dose for each insertion was 4.5 Gy - 4 x 4.5 = 18 Gy

ICRU 38 Bladder dose for each insertion was 5.0 Gy - 4 x 5.0 = 20 Gy

Vaginal mucosa dose for each insertion was 8.4 Gy - 4 x 8.4 Gy = 33.6 Gy

<table>
<thead>
<tr>
<th><strong>Point A (right)</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2. (^*) EBRT (physical dose)</td>
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</tr>
<tr>
<td>3. (^*) Nodal and/or parametrial boosts (physical dose)</td>
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<td>4. (^*) Brachytherapy (physical dose)</td>
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<tr>
<td>5. (^*) Total physical dose (EBRT + Boosts + Brachy)</td>
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<td>6. (^*) Total biological dose for HDR (EQD2)</td>
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<table>
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<td>7. (^*) EBRT (physical dose)</td>
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<tr>
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<td>9. (^*) Brachytherapy (physical dose)</td>
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<tr>
<td>10. (^*) Total physical dose (EBRT + Boosts + Brachy)</td>
<td>71.2</td>
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<tr>
<td>11. (^*) Total biological dose for HDR (EQD2)</td>
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<table>
<thead>
<tr>
<th><strong>HR-CTV (D90)</strong></th>
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</thead>
<tbody>
<tr>
<td>12. (^*) EBRT (physical dose)</td>
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<tr>
<td>13. (^*) Nodal and/or parametrial boosts (physical dose)</td>
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<td>14. (^*) Brachytherapy (physical dose)</td>
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<tr>
<td>15. (^*) Total physical dose (EBRT + Boosts + Brachy)</td>
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<td>16. (^*) Total biological dose for HDR (EQD2)</td>
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<table>
<thead>
<tr>
<th><strong>ICRU 38 Rectal Reference Point</strong></th>
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<tr>
<td>17. (^*) EBRT (physical dose)</td>
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<td>18. (^*) Nodal and/or parametrial boosts (physical dose)</td>
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<td>19. (^*) Brachytherapy (physical dose)</td>
<td>18</td>
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<tr>
<td>20. (^*) Total physical dose (EBRT + Boosts + Brachy)</td>
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<td>21. (^*) Total biological dose for HDR (EQD2)</td>
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<table>
<thead>
<tr>
<th><strong>ICRU 38 Bladder Reference Point</strong></th>
<th></th>
</tr>
</thead>
</table>
22. *EBRT (physical dose)  45
23. *Nodal and/or parametrial boosts (physical dose)  
24. *Brachytherapy (physical dose)  20
25. *Total physical dose (EBRT + Boosts + Brachy)  65
26. *Total biological dose for HDR (EQD2)  75.2

<table>
<thead>
<tr>
<th>Vaginal Mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td>27. *EBRT (physical dose)  45</td>
</tr>
<tr>
<td>28. *Nodal and/or parametrial boosts (physical dose)</td>
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<tr>
<td>29. *Brachytherapy (physical dose)  33.6</td>
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<tr>
<td>30. *Total physical dose (EBRT + Boosts + Brachy)  78.6</td>
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<td>31. *Total biological dose for HDR (EQD2)  119.</td>
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Mandatory for all sites to report Point A dose

It is optional for sites using image guided brachytherapy to report HR-CTV D90

For PDR – depending on the type of PDR, dose will be reported in either physical or biological dose at the discretion of the individual centre.
Sites using HDR BT and reporting dose in EQD2 should use:
\[ \alpha/\beta = 10 \text{ Gy} \] for Point A and HR-CTV
\[ \alpha/\beta = 3 \text{ Gy} \] for Rectal, Bladder and Vaginal Mucosa points
Example 4
EBRT + R pelvic nodal boost + HDR BT

EBRT: 45.00 Gy in 25 fractions
R pelvic nodal boost: 5.4 Gy in 3 fractions (Anterior-Posterior fields overlap with Right Point A)
HDR: 4 x 7.00 Gy prescribed to Point A
Point A dose for each insertion was: 7.00 Gy - 4 x 7.0 = 28 Gy
ICRU 38 Rectal dose for each insertion was: 4.5 Gy (64% of 7.00 Gy) 4 x 4.5 = 18 Gy
ICRU 38 Bladder dose for each insertion was: 5.0 Gy (71% of 7.00 Gy) 4 x 5.0 = 20 Gy
Vaginal mucosa dose for each insertion was 8.4 Gy (120% of 7.00 Gy) 4 x 8.4 = 33.6 Gy

<table>
<thead>
<tr>
<th>Point A (right)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>2.* EBRT (physical dose)</td>
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<tr>
<td>3.* Nodal and/or parametrial boosts (physical dose)</td>
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<td>5.* Total physical dose (EBRT + Boosts + Brachy)</td>
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<td>6.* Total biological dose for HDR (EQD2)</td>
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<table>
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<td>10.* Total physical dose (EBRT + Boosts + Brachy)</td>
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<td>11.* Total biological dose for HDR (EQD2)</td>
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<table>
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<tr>
<th>HR-CTV (D90)</th>
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<tbody>
<tr>
<td>12.* EBRT (physical dose)</td>
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<td>14.* Brachytherapy (physical dose)</td>
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<tr>
<td>15.* Total physical dose (EBRT + Boosts + Brachy)</td>
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<td>17.* EBRT (physical dose)</td>
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<td>19.* Brachytherapy (physical dose)</td>
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### ICRU 38 Bladder Reference Point

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<th>Description</th>
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<tr>
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<td>Total biological dose for HDR (EQD2)</td>
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<td>23.*</td>
<td>Nodal and/ or parametrial boosts (physical dose)</td>
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<td>24.*</td>
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</tr>
<tr>
<td>25.*</td>
<td>Total physical dose (EBRT + Boosts + Brachy)</td>
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<tr>
<td>26.*</td>
<td>Total biological dose for HDR (EQD2)</td>
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### Vaginal Mucosa

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<th>Description</th>
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</thead>
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<tr>
<td>27.*</td>
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<td>29.*</td>
<td>Brachytherapy (physical dose)</td>
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<tr>
<td>30.*</td>
<td>Total physical dose (EBRT + Boosts + Brachy)</td>
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<tr>
<td>31.*</td>
<td>Total biological dose for HDR (EQD2)</td>
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</table>

Mandatory for all sites to report Point A dose

It is optional for sites using image guided brachytherapy to report HR-CTV D90

For PDR – depending on the type of PDR, dose will be reported in either physical or biological dose at the discretion of the individual centre. 
Sites using HDR BT and reporting dose in EQD2 should use:
- $\alpha/\beta = 10$ Gy for Point A and HR-CTV
- $\alpha/\beta = 3$ Gy for Rectal, Bladder and Vaginal Mucosa points
4.2 Cisplatin chemotherapy

All patients in the study receive 5 cycles of cisplatin chemotherapy in conjunction with radiotherapy. Please refer to the current study protocol for dosage information. Chemotherapy administration should be as per local institutional standard protocol.

4.2.1 Cisplatin supply

Cisplatin (NSC #119875)

4.2.1.1 Formulation: Cisplatin is available in aqueous solution in 50 mg and 100 mg vials with 100 mg mannitol and 90 mg sodium chloride.

4.2.1.2 Preparation: Aluminum reacts with cisplatin causing precipitation formation and loss of potency, therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

4.2.1.3 Storage: The aqueous solution should be stored at room temperature and protected from light.

4.2.1.4 Adverse effects: Leukopenia, thrombocytopenia, anemia, nausea, vomiting, nephrotoxicity, ototoxicity, peripheral neuropathy, electrolyte imbalance, hypocalcemia, hypomagnesemia, aminoglycoside ototoxicity, ocular toxicity, and allergic reactions. Infrequent: Cardiac abnormalities, anorexia, elevated SGOT, rash, alopecia and acute myeloid leukemia.

NOTE: Aminoglycoside antibiotics given before, with, or after cisplatin may potentiate renal toxicity and should be avoided whenever possible.

Severe renal toxicity can be largely avoided by induction of a diuresis before, during and after treatment.

Mild renal dysfunction is a common complication (10%) of chronic therapy and may require discontinuation of therapy if creatinine > 1.5 x institutional upper limit normal (ULN).

Mild or severe electrolyte abnormalities may occur (5%) as acute or chronic complications, especially hypokalemia or hypomagnesemia. Monitoring of electrolytes and electrolyte replacement will usually correct these abnormalities. Rarely, severe hypomagnesemia and hypocalcemia may require replacement therapy and discontinuation of treatment with cisplatin.

Allergic reactions are rare. If accompanied by respiratory symptoms, allergic reactions require discontinuation of treatment.
Patch or skin tests are recommended for patients with suspected allergy to cisplatin. An emergency set for the treatment of allergic reactions should be available in the treatment area.

Local necrosis and thrombophlebitis can be avoided by careful administration.

Neurotoxicity may be related to cumulative dose and severe toxicity can be largely avoided by careful monitoring for evidence of paresthesias and timely discontinuation of treatment. Ataxia has been described.

Ototoxicity may occur.

**NOTE:** Eighth (VIII) nerve toxicity resulting in hearing loss and (less commonly) vestibular symptoms, is a well-documented complication of cisplatin treatment and is usually related to total cumulative dose. It is advised that patients placed on cisplatin, whether as a single agent therapy or combination, be questioned concerning hearing loss. Patients with a history of hearing loss should be considered for pre-treatment audiometry with follow-up audiometry as clinically indicated. It is recommended that patients be queried concerning hearing loss before each course of cisplatin.

4.2.1.5 Supplier: Commercially available. Consult package insert for complete product information.
5.0 ADJUVANT CHEMOTHERAPY

Patients randomised to the adjuvant chemotherapy arm receive 4 cycles of carboplatin/paclitaxel doublet chemotherapy. Please refer to the current study protocol for dosage information.

Chemotherapy administration and management of hypersensitivity to paclitaxel should be as per local institutional standard protocol.

5.1 Paclitaxel supply

5.1.1 Formulation: Paclitaxel is supplied as a 6mg/mL non-aqueous solution in multi dose vials containing 30mg/5mL, 100mg/16.7mL, or 300mg/50mL of paclitaxel. In addition to 6mg of paclitaxel, each mL of sterile non-pyrogenic solution contains 527mg of purified Cremophor® EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.

5.1.2 Storage: Unopened vials of paclitaxel are stable to the date indicated on the package when stored between 20 to 25°C (68 to 77°F). Protect from light.

5.1.3 Preparation: Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride for Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or 5% Dextrose in Ringer’s Injection to a final concentration of 0.3 to 1.2mg/mL. The solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C / 77°F) and room lighting conditions.

NOTE: In order to minimize patient exposure to the plasticizer DEHP, which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should be stored in bottles (glass, polypropylene) or plastic (polypropylene, polyolefin) bags and administered through polyethylene-lined administration sets.

Paclitaxel should be administered through an inline filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX- 2® or IVEX-HP®, which incorporate short inlet and outlet PVC-coated tubing, has not resulted in significant leaching of DEHP.

All patients should be premedicated with corticosteroids, diphenhydramine, and H₂ antagonists prior to paclitaxel administration in order to prevent severe hypersensitivity reactions.

Patients who experience reactions to drug may need to repeat the premedication and to be rechallenged with a dilute solution and slow infusion. Severe hypersensitivity reactions to paclitaxel do not have to proceed with a re challenge. Docetaxel may be substituted.

5.1.4 Adverse Effects: Consult the package insert for the most current and
5.1.5 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

5.2 Carboplatin Supply
(Paraplatin® - NSC #241240)

5.2.1 Formulation: Carboplatin is supplied as a sterile, pyrogen-free, 10mg/mL aqueous solution in multi-dose vials containing 50mg/5mL, 150mg/15mL, 450mg/45mL, or 600g/60mL of carboplatin.

5.2.2 Storage: Unopened vials of carboplatin are stable to the date indicated on the package when stored at 25°C (77°F). Excursions from 15 to 30°C (59 to 86°F) are permitted. Protect from light. Carboplatin multi dose vials maintain microbial, chemical, and physical stability for up to 14 days at 25°C following multiple needle entries.

5.2.3 Preparation: Carboplatin aqueous solution can be further diluted to concentrations as low as 0.5mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride for Injection, USP. When prepared as directed, carboplatin aqueous solutions are stable for 8 hours at room temperature (25°C / 77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution. Institutional pharmacy policy may allow refrigeration and longer storage.

NOTE: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

5.2.4 Adverse Effects: Consult the package insert for the most current and complete information.

5.2.5 Supplier: Commercially available both from Bristol-Myers Squibb Oncology as well as generic manufacturers. Consult the American Hospital Formulary Service Drug Information guide, Facts and Comparisons, or the package insert for additional information.

5.2.6 Dosing of Carboplatin (05/13/2013):

1) The Cockcroft-Gault formula will be used in GOG trials (not the Jelliffe formula).

2) Conversion of IDMS creatinine levels to “non-IDMS” values will not be permitted.
3) The carboplatin calculation tool on the GOG website has been updated. A legacy carboplatin calculator (using the Jelliffe formula and IDMS to “non-IDMS” conversion) is also available, if needed for dose modifications (see below).

**Dosing of Carboplatin: (05/13/2013)**

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using an estimated glomerular filtration rate (GFR) from the Cockcroft-Gault formula.

2) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

3) Carboplatin doses will be based on the subject’s weight at the time of start of adjuvant chemotherapy and will remain the same throughout the study. However, the doses will be recalculated if the patient has a weight change of greater than or equal to 10% from the time of start of adjuvant chemotherapy.

4) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using a minimum value of 0.7 mg/dl. If a patient is currently being dosed using a creatinine value less than 0.7 mg/dl, adjust dose with next planned treatment.

5) For trials where patients enter and are treated within less than or equal to 12 weeks of surgery: If a more appropriate (higher) baseline creatinine value is available from the pre-operative period (within 4 weeks of surgery date), that value may also be used for the initial estimation of GFR.

**CALVERT FORMULA:**
Carboplatin dose (mg) = target AUC x (GFR + 25)
NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
Maximum carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.
The maximum allowed doses of carboplatin are:
AUC 6 = 900 mg
AUC 5 = 750 mg
AUC 4 = 600 mg

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (ml/min) is calculated by the method of Cockcroft-Gault using the following formula:

\[
\text{Creatinine Clearance (mL/min)} = \frac{[140 - \text{Age (years)}] \times \text{Weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dl)}}
\]

**Notes:**
1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient. A BMI calculator is available at the following link: http://www.nhlbisupport.com/bmi/
   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.
   c. Adjusted weight should be used for estimation of GFR for patients with BMI of greater than or equal to 25.
   d. Adjusted weight calculation:
      \[
      \text{Ideal weight (kg)} = \left(\frac{\text{Height (cm)}}{2.54} - 60\right) \times 2.3 + 45.5
      \]
      \[
      \text{Adjusted weight (kg)} = ((\text{Actual weight} - \text{Ideal weight}) \times 0.40) + \text{Ideal weight}
      \]
   e. If a patient with BMI of greater than or equal to 25 is currently being dosed using actual weight, adjust dose with next planned treatment.

2) The Cockcroft-Gault formula above is specifically for women (it includes the 0.85 factor).

At the time of a dose modification for toxicity:
1) If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

2) If the dose of carboplatin (mg) at the time of dose modification, is higher than the previous dose due to the use of the Cockcroft-Gault formula [when the previous dose was calculated using the Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)], use the same method that was used to calculate the previous dose [Jelliffe formula and IDMS to “non-IDMS” conversion (if applicable)], to calculate the dose of carboplatin (mg) at the time of dose reduction. A legacy carboplatin calculator is available on the GOG website for this purpose. This will ensure that the patient is actually receiving a dose reduction.

3) For patients who undergo a second dose reduction (dose level -2) the dose should be calculated as a 10% reduction in the milligram dose used for dose level -1.
6.0 SUB-STUDY – Translational Component (GOG and RTOG) (05/13/2013)

GOG-0274 Specimen Procedures

6.1 Translational Research Objective

GOG and/or RTOG will evaluate and validate predictive and prognostic biomarkers, profiles, tests, and algorithms associated with treatment efficacy (response or failure), disease progression, survival or adverse events, and participate in consortium-type translational research including pharmacogenomic and pharmacogenetic studies.

6.2 Summary of Specimen Requirements

If the patient gives permission for her specimens to be collected and used for this optional translational research component, then participating institutions within the United States are required to submit the patient’s specimens as outlined below (unless otherwise specified).

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<th>Required Specimen (Specimen Code)</th>
<th>Collection Time Point</th>
<th>Ship To</th>
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</thead>
<tbody>
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<td>FFPE Primary Tumor (FP01)*</td>
<td>Prior to all treatment</td>
<td>GOG Tissue Bank within 8 weeks of registration¹</td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: 15 unstained slides (charged, 5µm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FFPE Metastatic Tumor (FM01)*</td>
<td>Prior to all treatment</td>
<td>GOG Tissue Bank within 8 weeks of registration¹</td>
</tr>
<tr>
<td>1st Choice: block</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd Choice: 15 unstained slides (charged, 5µm)</td>
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<td></td>
</tr>
<tr>
<td>Whole Blood (WB01) 7-10mL drawn into purple top (EDTA) tube(s)</td>
<td>Prior to or after starting study treatment</td>
<td>GOG Tissue Bank the day the specimen is collected¹</td>
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<tr>
<td>Pre-1st Cisplatin Infusion Plasma (PB01)</td>
<td>Prior to 1st cisplatin infusion</td>
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<tr>
<td>prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)</td>
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<td>Pre-2nd Cisplatin Infusion Plasma (PB02)</td>
<td>Prior to 2nd Cisplatin Infusion</td>
<td>GOG Tissue Bank within 9 weeks of registration¹</td>
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<tr>
<td>prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-3rd Cisplatin Infusion Plasma (PB03)</td>
<td>Prior to 3rd cisplatin infusion</td>
<td></td>
</tr>
<tr>
<td>prepared from 7-10mL of blood drawn into purple top (EDTA) tube(s)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the GOG Tissue Bank

GOG Tissue Bank / Protocol GOG-0274, Nationwide Children’s Hospital, 700 Children’s Drive, WA1340, Columbus, OH 43205. Phone: (614) 722-2865, FAX: (614) 722-2897, Email: GOGBank@nationwidechildrens.org

6.3 Obtaining a Bank ID
Only one GOG Bank ID (# # # # - # # - G # # #) is assigned per patient. All specimens and accompanying paperwork must be labeled with this coded patient number. A GOG Bank ID can be obtained online via the Tissue Bank Portal on the GOG website (under Tools on the Web Menu page).

Obtain the patient's study ID (GOG #) for all protocols with specimen requirements before requesting a Bank ID from the Tissue Bank Portal. Be sure to indicate if the patient has a previous GOG # when registering. This will ensure that the patient is only assigned one Bank ID.

The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID. To lookup an existing Bank ID, enter the patient's GOG # and click Lookup Bank ID. To lookup GOG # (s) associated with a given Bank ID, enter the Bank ID (without dashes) and click Lookup GOG #.

Please contact User Support at the GOG Statistical and Data Center if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

6.4 Requesting Specimen Kits

6.4.1 Ordering Specimen Kits

Specimen kits can be ordered online via the Kit Management link on the GOG website (under Data Entry on the Web Menu page). Each site may order two kits per protocol per day (daily max = 6 kits).

Please contact the GOG Tissue Bank if you need assistance (GOGBank@nationwidechildrens.org; Phone: (866) 464-2262).

Please plan ahead to allow time for kits to be shipped by ground transportation.

6.4.2 Materials Provided in the Specimen Kits

One specimen kit will be provided per patient for the collection and shipment of frozen plasma specimens. Each kit will consist of:

- dual-chamber shipping container
- thirty cryovials
- three transfer pipettes
- three 15mL conical tubes
- two secondary shipping envelopes with absorbent material
- two Tyvek envelopes
- dry ice label (UN1845)
6.4.3 Unused Materials and Specimen Kits

Unused materials and specimen kits should be returned to the GOG Tissue Bank. Contact the bank if you have any questions about the return of unused materials.

6.5 Submitting Formalin-Fixed and Paraffin-Embedded Tissue

6.5.1 Requirement

*If the patient gives permission for her specimens to be used for this optional translational research component, then the participating institution is required to submit specimens as outlined in Section 6.2 above.*

Formalin-fixed and paraffin-embedded (FFPE) tissue should be the most representative of the specimen type (primary [FP01], metastatic [FM01]).

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 15 unstained slides (charged, 5µm) should be submitted. All tissue sections should be cut sequentially from the same block.

The type of specimen (block or slides) should be specified on Form SP.

All FFPE tissue should be submitted with the corresponding pathology report.

6.5.2 Purpose

FFPE will be used to fulfil the objective stated in Section 6.1 above.

6.5.3 Time Points

Primary (FP01) and metastatic (FM01) tumor should be collected prior to starting all treatment.

6.5.4 Format for Labeling the Specimen

A waterproof permanent marker or printed label should be used to label each specimen with:

- GOG Bank ID (###-#-G###)
- GOG protocol number (GOG0274)
specimen code (FP01 for primary, FM01 for metastatic)  
collection date (mm/dd/yyyy)  
surgical pathology accession number  
block number  

When labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

6.6 Submitting Whole Blood

6.6.1 Requirement

If the patient gives permission for her specimens to be used for this optional translational research component, then the participating institution is required to submit specimens as outlined in Section 6.2 above.

A lavender/purple top (EDTA) tube should be used for whole blood collection.

The type of blood collection tube (EDTA) should be specified on Form SP.

6.6.2 Purpose

Whole blood will be used to fulfil the objective stated in Section 6.1 above.

6.6.3 Time Points

Whole blood can be collected at any time prior to or after starting study treatment.

6.6.4 Format for Labeling the Specimen

A waterproof permanent marker or printed label should be used to label each specimen with:

GOG Bank ID (# # # - # # - G # # #)  
GOG protocol number (GOG0274)  
specimen code (WB01)  
collection date (mm/dd/yyyy)

6.6.5 Instructions for Preparing the Specimen

1. Label the lavender/purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.
2. Draw 7-10mL of blood into the labeled lavender/purple top tube(s). A minimum of 3mL is needed for processing.

3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and EDTA.

4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to the GOG Tissue Bank the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

6.7 Submitting Plasma

6.7.1 Requirement

*If the patient gives permission for her specimens to be used for this optional translational research component,* then the participating institution is required to submit specimens as outlined in Section 6.2 above.

A lavender/purple top (EDTA) tube should be used for blood collection to prepare plasma.

The type of blood collection tube (EDTA) should be specified on Form SP.

6.7.2 Purpose

Plasma will be used to fulfil the objective stated in Section 6.1 above.

6.7.3 Time Points

Three plasma specimens are required. Plasma should be collected:

1. prior to starting cycle 1 of study treatment (PB01),
2. prior to starting cycle 2 of study treatment (PB02), and
3. prior to starting cycle 3 of study treatment (PB03).

6.7.4 Format for Labeling the Specimen

A waterproof permanent marker or printed label should be used to label each specimen with:

GOG Bank ID (# # # # - # # - G # # #)
GOG protocol number (GOG0274)
specimen code (PB##, see above)
6.7.5 Instructions for Preparing the Specimen

1. Label cryovials and a 15mL conical tube as described above. Use 2mL cryovials if plasma will be shipped to the GOG Tissue Bank.

2. Draw 7-10mL of blood into lavender/purple top (EDTA) tube(s).

3. Immediately after collection, gently invert the blood collection tube 5-10 times to mix the blood and EDTA.

4. Centrifuge the blood at 1000g for 15 minutes at 4°C (preferred) or room temperature to separate the plasma (top, straw-colored layer) from the red blood cells (bottom, red layer).

5. Transfer the plasma into a pre-labeled 15mL conical tube and gently mix.

6. Quickly, evenly dispense (aliquot) the plasma into the pre-labeled cryovials and cap the tubes securely. Place a minimum of 0.25mL into each cryovial.

7. Immediately freeze the plasma in an upright position in a -70°C to -80°C freezer or by direct exposure with dry ice until ready to ship. If a -70°C to -80°C freezer is not available for storage, store and ship on dry ice within 24 hours of collection. 

database please email the study mailbox at outback@ctc.usyd.edu.au.” has been added to this section.

6.8 GOG Specimen Form (Form SP) Reporting Requirements

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Due within</th>
<th>Copies</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specimen Consent Application</td>
<td>1</td>
<td>Registration</td>
<td>N/A</td>
</tr>
<tr>
<td>Form SP-FP01-0274 FFPE primary tumor</td>
<td>8</td>
<td>Registration</td>
<td>N/A</td>
</tr>
<tr>
<td>Form SP-FM01-0274 FFPE metastatic tumor</td>
<td>8</td>
<td>Registration</td>
<td>N/A</td>
</tr>
<tr>
<td>Form SP-WB01-0274 whole blood</td>
<td>8</td>
<td>Registration</td>
<td>N/A</td>
</tr>
<tr>
<td>Form SP-PB01-0274 Pre-1st cisplatin infusion</td>
<td>9</td>
<td>Registration</td>
<td>N/A</td>
</tr>
<tr>
<td>Form SP-PB02-0274 Pre-2nd cisplatin infusion</td>
<td>9</td>
<td>Registration</td>
<td>N/A</td>
</tr>
<tr>
<td>Form SP-PB03-0274 Pre-3rd cisplatin infusion</td>
<td>9</td>
<td>Registration</td>
<td>N/A</td>
</tr>
</tbody>
</table>

/ Form SP must be submitted regardless of whether the specimen is submitted for research.

6.8.1 SP Form Requirements

Form SP must be completed and submitted online to the GOG Statistical and Data Center (SDC) using the SDC Electronic Data Entry System (SEDES). Form SP must be submitted for each
specimen required for the protocol regardless of whether the specimen is submitted for research.

Forms for required specimens will automatically load on the patient’s form schedule. If optional specimens will be submitted, the forms can be added using the Optional Form Load feature on the patient’s form schedule.

Specific instructions for completing Form SP are available via SEDES by scrolling down to the SP Forms for the specific protocol.

6.8.2 Instructions for Submitting Form SP Online

Form SP must be submitted online using SEDES which is available on the GOG Web Menu under Registration/Data Entry. A copy of the completed form must also accompany each specimen shipped to the GOG Tissue Bank. Retain a printout of the completed form for your records. Form SP does not need to be sent to the GOG Tissue Bank when specimens are not collected.

To access Form SP for online submission, log onto the GOG Web Menu and use SEDES to electronically enter Form SP data. Any questions about access or problems should be directed to the User Support at the GOG Statistical and Data Center (Email: support@gogstats.org; Phone: 716-845-7767).

6.9 Shipping Specimens

6.9.1 FFPE

FFPE tissue and a copy of the corresponding pathology report should be shipping using your own container at your own expense to:

GOG Tissue Bank / Protocol GOG-0274  
Nationwide Children’s Hospital  
700 Children’s Drive, WA1340  
Columbus, OH 43205  
Phone: (614) 722-2865  
Fax: (614) 722-2897  
E-mail: GOGBank@nationwidechildrens.org

Do not ship FFPE for Saturday delivery.

6.9.2 Whole Blood

All whole blood should be shipped to the GOG Tissue Bank (address above).
Whole blood specimens can be shipped to the GOG Tissue Bank **Monday through Friday for Tuesday through Saturday delivery**. Please do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via **FedEx priority overnight**.

When shipping whole blood specimens, please be aware that your institution must comply with IATA standards (www.iata.org). If you have questions regarding your shipment, contact the GOG Tissue Bank.

To ship whole blood specimens you will need a sturdy shipping container (e.g., a cardboard or styrofoam box), a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), an Exempt Human Specimen Sticker, and a pre-paid FedEx air bill.

*If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.

If you do not have these materials available at your institution, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484, Website: [www.saftpak.com](http://www.saftpak.com)).

**Instructions for Shipping Whole Blood Using Your Own Shipping Container**

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.

2. Wrap the biohazard envelope in bubble wrap or another padded material.

3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.

4. Place the Tyvek envelope in a sturdy shipping contained (e.g., cardboard FedEx box).

5. Insert a copy of the SP Form(s) into the box.

6. Attach an Exempt Human Specimen Sticker to the outside of the shipping container.
7. Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

8. Make arrangements for FedEx pick-up through your usual institutional procedure or by calling 800-238-5355.

6.9.3 Plasma

Frozen plasma should be shipped using the specimen kit provided to the GOG Tissue Bank (address above).

Frozen specimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen specimens on Friday or the day before a holiday. Please note, Saturday delivery is not available for frozen specimens.

Frozen specimens should be stored in an ultra-cold freezing/storage space (i.e., ultra cold ≤-70°C freezer, liquid nitrogen, or direct exposure with dry ice) until the specimens can be shipped.

**Instructions for Shipping Frozen Specimens in a Dual Chamber Specimen Kit**

1. Pre-fill each chamber of the specimen kit about 1/3 full with dry ice.

2. Place the frozen specimens from each time point in a separate zip-lock bag.

3. Divide the zip-lock bags between the two biohazard envelopes containing absorbent material. Do not place more than 25 vials in each biohazard envelope. Put each secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing all envelopes.

4. Place one Tyvek envelope containing frozen specimens into each chamber of the kit and fill the chamber to the top with dry ice.

5. Insert the SP Forms. (Forms may be inserted between the inner and outer chambers of dual chamber kits.)

6. Place the foam cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner (foam) chambers.
Print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Attach the air bill.

8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.

9. Arrange for FedEx pick-up through your usual Institutional procedure or by calling 800-238-5355.

6.10 Banking Specimens for Future Research

Specimens will remain banked in the GOG Tissue Bank and made available for approved research projects if the patient has provided permission for the use of her specimens for future cancer and/or non-cancer research. The patient’s choices will be recorded on the signed informed consent document and electronically via the online Specimen Consent Application. At the time of specimen selection for project distribution, the most recent consent information will be used.

**GOG Institutions can amend a patient’s choices regarding the future use of her specimens at any time if the patient changes her mind.**

If the patient revokes permission to use her specimens, the GOG Tissue Bank will destroy or return any remaining specimens to insure the patient’s wishes are honored. The patient’s specimens will not be used for any further research; however, any specimens distributed for research prior to the revoking of consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens prior to revoking consent.

Please note, when return of specimens is requested, shipping will be at the expense of the submitting institution.

**RTOG-1174 Translational Component**

6.11 RTOG Translational Component for RTOG 1174

RTOG Member Institutions: RTOG Patient Study IDs will be assigned by the RTOG after the patient is re-registered with RTOG as specified in section 3.

6.11.1 RTOG Tissue/Specimen Submission

The RTOG Biospecimen Resource at the University of California San Francisco acquires and maintains high quality specimens from RTOG trials. Tissue from each block is preserved through careful block storage and processing. The RTOG encourages participants in protocol studies to consent to the banking of their
tissue. The RTOG Biospecimen Resource provides tissue specimens to investigators for translational research studies. Translational research studies integrate the newest research findings into current protocols to investigate important biologic questions.

In this study, tissue will be submitted to the RTOG Bio-specimen Resource for the purpose of tissue banking and future translational research.

6.11.2 RTOG Specimen Collection for Tissue Banking and Translational Research

For patients who have consented to participate in the tissue/blood component of the study, the following must be provided in order for the case to be evaluable for the Biospecimen Resource:

- One H&E stained slide of the primary tumor, and when available from the metastatic tumor
- A paraffin-embedded tissue block of the primary tumor or 15 five micron unstained sections cut onto positively charged slides of tumor tissue (Note: the FFPE block or unstained slides must correspond with the H&E slide)
- When available a paraffin-embedded tissue block of the metastatic tumor or 15 five micron unstained sections cut onto positively charged slides of tumor tissue (Note: the FFPE block or unstained slides must correspond with the H&E slide)
- Blocks and/or slides must be clearly labeled with the pathology identification number that corresponds to the Pathology Report.
- A Pathology Report documenting that the submitted block(s) or slides contain tumor. The report must include the RTOG protocol number and patient’s case number. The patient’s name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.
- A Specimen Transmittal (ST) Form clearly stating that tissue is being submitted for the RTOG Biospecimen Resource; if for translational research, this should be stated on the form. The form must include the RTOG protocol number and patient’s case number.

Plasma and whole blood collection: For detailed processing and shipping instructions, see Section 6.11.7

The following materials must be provided to the RTOG Biospecimen Resource: A Specimen Transmittal Form documenting the date of collection of the biospecimen;
the RTOG protocol number, the patient’s case number, time point of study, and method of storage, for example, stored at -80° C, must be included. The specimens to be provided are:

- 5-10 mL of anticoagulated whole blood in EDTA tube #1 (purple/lavender top) taken from patient and processed for collection of plasma. This sample is to be obtained three times. Once prior to the first cisplatin infusion, once prior to the second cisplatin infusion, and once prior to the third cisplatin infusion.

- 5-10 mL of anticoagulated whole blood in EDTA tube #2 (purple/lavender top) taken from patient for collection of DNA. This sample is to be obtained once prior to treatment. However, if the site missed this collection time point, they may collect whole blood at any time point or during a follow-up visit. No additional samples are to be obtained.

6.11.3 Storage Conditions

Freeze Blood and Plasma aliquots in a -80° C Freezer on Dry Ice or snap freeze in liquid nitrogen. Store frozen biospecimens at -80° C (-70°C to -90°C) until ready to ship. If a -80°C Freezer is not available:

- Samples can be stored short term in a -20° C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday)

OR:

- Samples can be stored in plenty of dry ice for up to one week, replenishing daily (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

OR:

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday).

Please indicate on Specimen Transmittal Form the specific storage conditions used.

6.11.4 Specimen Collection Summary (05/13/2013)

<table>
<thead>
<tr>
<th>Specimens for Tissue Banking/Translational Research</th>
<th>Collected when:</th>
<th>Submitted as:</th>
<th>Shipped:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Representative H&amp;E stained slide of the primary tumor,</td>
<td>Prior to treatment</td>
<td>H&amp;E stained slide</td>
<td>Slide shipped ambient</td>
</tr>
</tbody>
</table>
### Corresponding paraffin-embedded tissue block of the primary tumor
- **Before initiation of treatment:**
  - 15 five micron unstained slides cut on positive charged slides
- **When available:**
  - An H&E slide and corresponding FFPE block (or 15 unstained slides) from the metastatic tumor

### PLASMA
- **5-10 mL of anticoagulated whole blood in EDTA tube #1 (lavender top)**
  - Centrifuged for plasma
  - Three times:
    1. Prior to 1st cisplatin infusion
    2. Prior to second cisplatin infusion
    3. Prior to third cisplatin infusion
- **Frozen plasma samples containing 0.5 mL per aliquot in 1 mL cryovials (five to ten)**
  - Plasma sent frozen on dry ice via overnight carrier (Mon-Wed)

### DNA
- **5-10 mL of anticoagulated whole blood in EDTA tube #2 (lavender top)**
  - Mixed and aliquoted (not centrifuged)
  - Once:
    - Prior to treatment 1.
    - **Note:** If this collection is missed, the site may collect whole blood for DNA at any time point or follow up visit.
- **Frozen whole blood samples containing 1ml per aliquot in 1 mL cryovials (three to five)**
  - Whole blood sent frozen on dry ice via overnight carrier (Mon-Wed)

### Submit materials for Tissue Banking and Translational Research
To the appropriate address:

*(All FedEx/UPS packages, including ALL frozen specimens)*

**RTOG Biospecimen Resource**
University of California San Francisco
2340 Sutter St, Rm S341
San Francisco, CA 94115

**U.S. Postal Service Mailing Address:** (USPS only; non-urgent documents and pathology)

RTOG Biospecimen Resource
University of California San Francisco
Campus Box 1800
2340 Sutter St, Rm S341
San Francisco, CA 94143-1800

- Include all RTOG paperwork in pocket of biohazard bag.
- Check that the ST form has the consent boxes checked off.
o Check that all samples are labelled with RTOG study and case number, date of collection and specimen type.

Questions: 415-476-7864 FAX 415-476-5271; RTOG@ucsf.edu

6.11.5 FFPE Specimens:

- Slides should be shipped in a plastic slide holder/slide box. Place a small wad of padding in top of container if you can hear the slides rattling they are likely to break during shipping.
- FFPE Blocks can be wrapped with paper, or placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that the blocks do not rattle when the box is shaken. If you can hear them rattling they are likely to break during shipping. Use of cold packs is highly recommended during the summer months.
- Slides and Blocks can be shipped ambient or with a cold pack either by USPS to the USPS address (94143) or by courier to our street address (94115). Do NOT ship slides and blocks on dry ice.

6.11.6 Frozen Specimens:

- Multiple cases may be shipped in the same cooler, but make sure each case is in a separate bag and each vial is labelled with the RTOG study and case numbers, date of collection and specimen type.
- Place specimens and absorbent shipping material in Styrofoam cooler filled with dry ice (at least 7 lbs). There should be plenty of dry ice under and above the specimens. If the volume of specimens is greater than the volume of dry ice then ship in a larger Styrofoam box, or two separate boxes. Any Styrofoam box can be used, as long as it is big enough.
- Specimens received thawed due to insufficient dry ice or shipping delays will be discarded and the site will be notified.
- Send frozen specimens via overnight courier to the address above. Specimens should only be shipped Monday through Wednesday (Monday-Tuesday for Canada) to prevent thawing due to delivery delays. Saturday or holiday deliveries cannot be accepted. Samples can be stored frozen at -80C until ready to ship.

For Questions regarding collection/shipping or to order a Frozen Biospecimen Collection Kit, please contact the RTOG Biospecimen Resource by email at: RTOG@ucsf.edu or call 415-476-RTOG (7864)
6.11.7 Preparation and Processing of Plasma and Whole Blood:

**PLEASE MAKE SURE THAT EVERY SPECIMEN IS LABELED, and include collection time point on STF.**

**A) Plasma): Purple Top EDTA tube #1**

- Label as many 1ml cryovials (5 to 10) as necessary for the plasma collected. **Label them with the RTOG study and case numbers, and collection date,**, and clearly mark cryovials “plasma”.

**Process:**
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA.
2. Centrifuge specimen(s) within one hour of collection in a standard clinical centrifuge at ~2500 RPM for 10 minutes at 4°C (preferred). If sites are unable to process samples at 4°C then spinning at room temperature is acceptable if done within 2 hours of draw but must be noted on the STF.
3. If the interval between specimen collection and processing is anticipated to be more than one hour, keep specimen on ice until centrifuging is performed.
4. Carefully pipette and aliquot 0.5 ml plasma into as many cryovials as are necessary for the plasma collected (5 to 10). Avoid pipetting up the buffy coat layer.
5. Place cryovials into biohazard bag and immediately freeze at -70° to -90°C
6. Store frozen plasma -70 to -90°C until ready to ship on dry ice.
7. See 6.13.3 for storage conditions.

**B) Whole Blood For DNA: Purple Top EDTA tube #2**

- Label as many 1ml cryovials (3 to 5) as necessary for the whole blood collected. **Label them with the RTOG study and case number, collection date/ time, and clearly mark cryovials “blood”**.

**Process: (05/13/2013)**
1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot 1.0 ml blood into as many cryovials as are necessary for the blood collected (3 to 5).
3. Place cryovials into biohazard bag and freeze immediately at -70° to -80° Celsius.
4. Store blood samples frozen -70° to -90° C until ready to ship on dry ice.
5. See 6.11.3 for storage conditions.

Shipping/Mailing:

- Ship specimens on Dry Ice overnight Monday-Wednesday (Monday-Tuesday from Canada) to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all RTOG paperwork in a sealed plastic and tape to the outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). Add padding to avoid the dry ice breaking the tubes.
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 stickers to outer cardboard box.
- Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice. Add padding to avoid the dry ice from breaking the tubes.
- For questions regarding collection, shipping or to order a Blood Collection Kit, please Email: RTOG@ucsf.edu or call (415)476-7864.

6.11.8 Reimbursement

With the start of the new NCI National Clinical Trials Network (NCTN) Program, NCI funds for reimbursement for protocol-specified biospecimen materials will be distributed per the requirements/methods specified by the new NCTN Program.

6.11.9 Confidentiality/Storage


6.11.9.1 Upon receipt, the specimen is labelled with the RTOG protocol number and the patient’s case number only. The RTOG Biospecimen Resource database only includes the following information: the number of specimens received, the date the specimens were received, documentation of material sent to a qualified investigator, type of material sent, and the date the specimens were sent to the investigator. No clinical information is kept in the database.
6.11.9.2 Specimens for tissue banking will be stored for an indefinite period of time. Trial participants will be invited to donate specimens for tissue banking and to consent to store these indefinitely for future translational studies. If at any time the patient withdraws consent to store and use specimens, the material will be returned to the institution that submitted it.
7.0 DATA COLLECTION  (05/13/2013)

The data will be reported on electronic case report forms (eCRFs) using an InForm database. All site staff will be trained in the system used for electronic data capturing by the GCIG coordinating centre. The database is built and maintained by the NHMRC CTC.

NOTE: If at any time you are experiencing difficulty accessing the OUTBACK database please email the study mailbox at outback@ctc.usyd.edu.au.

7.1 eCRF General instructions

Source Documentation

All data entered on eCRFs should be verifiable from a source document. Source documents are those documents on which patient information is first recorded and includes, but is not limited to, lab results, the results of CT scans and patient medical records. To be considered a source document, the document must be signed and dated by the individual completing it. Each page of a source document should uniquely identify the patient.

Quality of Life (QOL) questionnaires are completed by the patient alone and do not require source documentation.

General Instructions for Form Completion

Do not leave blank fields, unless instructed to do so in the guidelines.

Select the following comments from the comment section:

- **Unknown** - when information is unobtainable
- **Not Done** - if measure has not been taken or test has not been performed
- **Not Applicable** - if measure was not due to be taken at the time of eCRF completion

** If the Unknown, Not Done or Not Applicable comment is selected, please specify WHY the data is Unknown, Not Done or Not Applicable in the ‘Comment’ section.

Patient Initials

Record the patient’s first, middle and last initial. If the patient does not have a middle initial, record a dash (-); record initials consistently throughout all trial documents.

Example

<table>
<thead>
<tr>
<th>Patient name</th>
<th>First name (f)</th>
<th>Middle name (m)</th>
<th>Last name (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jane Mary Smith</td>
<td>J</td>
<td>M</td>
<td>S</td>
</tr>
<tr>
<td>Jane Smith</td>
<td>J</td>
<td>-</td>
<td>S</td>
</tr>
</tbody>
</table>
### Institution

Record the name of your institution/hospital. The institution name should correspond to the institution the patient was enrolled by, unless the patient has transferred to another hospital conducting the OUTBACK study. Please refer to Section 3.6 on patient transfers.

### Rounding

Report all laboratory results rounded to the number of decimal places allowed on the eCRF, e.g. a neutrophil value of $4.72 \times 10^9/l$ would be reported as $4.7 \times 10^9/l$.

If your laboratory provides an integer value, but the CRF requires a decimal place, enter 0 as the decimal place (e.g. a value of 17 would be reported as 17.0 on the CRF).

### Units

Report all laboratory results in units specified on the eCRF.

For some laboratory results (Serum creatinine, haemoglobin, bilirubin, blood glucose) more than 1 unit can be selected.

### Source documents

It will be necessary to retain all relevant source documents at the site. When forwarding a copy of a source document to the NHMRC CTC (i.e. a hospital discharge report), please black out all patient identifiers with a thick black pen including the patient’s name (leaving the initials as required), medical record number and phone numbers and addresses. Please also ensure that any identifiers within the body of the report/document have also been masked appropriately.

Each page of all reports/documents sent to the NHMRC CTC should be clearly marked with the patient’s study number, initials and hospital name.

### Guidelines for transferring a patient

Throughout the duration of the trial it is possible that patients will move out of the area serviced by their local site conducting the OUTBACK study. If they are transferring to another area serviced by a site conducting the OUTBACK study, then responsibility for follow-up can be transferred to the new centre. If there is no site conducting the OUTBACK study nearby, then the follow-up should be maintained by the enrolling site. Please contact the OUTBACK study team if you wish to transfer a patient.

<table>
<thead>
<tr>
<th>Patient name</th>
<th>First name (f)</th>
<th>Middle name (m)</th>
<th>Last name (l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jane Smith-Jones</td>
<td>J</td>
<td>-</td>
<td>S</td>
</tr>
<tr>
<td>Jane McCall</td>
<td>J</td>
<td>-</td>
<td>M</td>
</tr>
</tbody>
</table>
Data requests (05/13/2013)
The NHMRC CTC will raise queries as necessary after reviewing eCRFs, and send out overdue form reports to the GOG and RTOG Data Centers for distribution to sites on a regular basis.

Queries
Queries should be responded to within 2 weeks of being raised on the eCRF.

Responding To Data Queries
- Locate open queries by either the query listing or by going to red lights on the time and events schedule.
- First correct any incorrect data and complete missing data items on the eCRF, and then select the reason for change and click the submit button.
- If the data item is missing because an answer is unknown please select Unknown from the comment section of the field. If the data item is missing because a test was not done, please select ‘Not Done’ from the comment section of the field. If the original data on the eCRF is confirmed to be correct, please select the ‘Original value is correct’ option on the query.
- To clarify data, please add a comment in the Comment section of eCRF field.

Overdue form reports
Overdue Reports will be sent to GCIG coordinating centres for distribution to local sites that have overdue forms. All outstanding items listed on these reports are to be answered as soon as possible. If sites are having problems with form completion or query resolution they should contact the GCIG coordinating office for assistance.

7.2 eCRF Specific instructions (05/13/2013)
Specific e-CRF completion guidelines are available to aid with data entry. They can be obtained from the GOG/RTOG website or data office.

7.3 Instructions for completing QOL forms (05/13/2013)
Patient questionnaires (Quality of Life) will be completed on paper throughout the OUTBACK study. The Quality of Life (QOL) questionnaire is available for downloading from the GOG and RTOG websites. Completed questionnaires should be scanned and emailed to the NHMRC CTC. Alternatively, questionnaires can be sent by regular mail. The email address and mailing address are provided in Section 1 of this Study Handbook. When sending the questionnaires by regular mail, please keep photocopies at site for your records. Completed questionnaires should not be faxed due to potential issues with legibility.

The aim of the quality of life component of the OUTBACK study is to assess the impact of treatment on patients. While QOL is a secondary outcome of the study, the ability of patients to cope with treatment is an important consideration. Quality of Life questionnaires, in addition to toxicity information, provides important data for clinicians considering the best treatment for their individual patients.

Each patient will complete the following Quality of Life Questionnaires:
QOL forms completion timeline

The time points for questionnaire completion are:

(Please also refer to the Schedule of Assessments in the current protocol)

- Baseline
- Beginning of adjuvant chemo cycle 1 (Arm B only)
- Beginning of adjuvant chemo cycle 2 (Arm B only)
- Beginning of adjuvant chemo cycle 3 (Arm B only)
- Beginning of adjuvant chemo cycle 4 (Arm B only)
- End of treatment
  (after chemoradiation for Arm A, after adjuvant chemo for Arm B)
- Follow-up 6 months
- Follow-up 9 months
- Follow-up 12 months
- Follow-up 15 months
- Follow-up 18 months
- Follow-up 21 months
- Follow-up 24 months
- Follow-up 30 months
- Follow-up 36 months

QOL Forms Completion Guidelines

All parts of the questionnaires must be completed by the patient, except for the cover page and header data.

A black, ball-point pen should be used to complete Quality of Life questionnaires.

**Before** giving the forms to the patient, please complete the following on each questionnaire:

- ANZGOG Patient number and Visit number
- ANZGOG Institution number
- Participant initials: First, middle and last initial
- Date of birth (format is DD/MM/YYYY)
- Date form completed (format is DD/MM/YYYY)

Questionnaires should be given to each patient as soon as possible after arrival in the clinic, to allow completion of all forms and collection before the patient leaves the clinic. At the first visit, the patient should be instructed to seek help or further instructions if she has any problems understanding or completing the form.
**These are patient-rated questionnaires.** The patient must hold the pen and choose the circle/complete the numbers themselves. QOL questionnaires should not be completed using an interpreter.

**Acceptable assistance is:**

- Further explanation about how to complete the form
- Reading instructions and questions aloud for patients with visual or reading difficulty
- Prompting for correction if the form has been incorrectly completed or is incomplete
- Prompting for return of form

Under no circumstances may family members, the clinician or data manager/trial coordinator complete the form, even at the request of the patient. Patients may prefer to complete the form in private. If at all possible, it is helpful to have a room with a desk available where practical.

Questionnaires should be completed before diagnostic procedures and treatment administration whenever possible to prevent any confounding effect.

Check that one number per line has been circled. Ask the patient to complete any missing numbers. If two or more numbers have been circled, please ask the patient to choose between the available options.

Check that the patient has used circles rather than any another symbol. Ask for any corrections.

Check that the patient has not circled numbers in columns over two or more lines. Even if they want to use the same number for several answers, each line should be circled individually. Ask for any corrections.

After completion of the questionnaire, please check that each question has been completed before the patient leaves the department.

If a patient does not complete a QOL questionnaire for a given time point, sites need to provide a reason for non-completion in the InForm database.
8.0 SERIOUS ADVERSE EVENT REPORTING (05/13/2013)

NOTE: All GOG and RTOG sites MUST report serious adverse events (SAEs) to both NHMRC CTC using the procedures set forth below (See Section 8.2) and CTEP using the CTEP-AERS reporting mechanism (See Section 8.3).

8.1 Definitions for SAE Reporting
All investigators will use the same definitions for NHMR CTC reporting as defined in the current study protocol (Section 9.3.1).

For CTEP and CTEP-AERS reporting, you must use the guidelines outlined below in Section 8.3.

8.2 NHMRC CTC Reporting procedure
In the case of a Serious Adverse Event the investigator must immediately report the event as follows (process must be completed within 24 hours of your awareness of the event).

TO REPORT AN INITIAL SAE:
1) Log into InForm and navigate to the relevant chemotherapy cycle. Trigger the SAE eCRF by answering the SAE “Yes/No” question with “Yes”
2) Click ‘New’ on the SAE tab
3) Complete the SAE Form* and Submit (tip: you can click submit at any time – data can be entered gradually as you locate the relevant information)
4) Once the Investigator has reviewed the SAE and the SAE is complete (no yellow fields or red data queries), click ‘Add Entry’ in the Report Details section (item 20). Enter today’s date, select report type Initial, enter the name of the Investigator who has reviewed the SAE, and enter Yes for ‘Report is complete, authorised and ready for submission’.
   An email notification will automatically be sent to the CTC when ‘Report is complete, authorised and ready for submission’ is submitted as Yes.
   NB: If the Report Details section is not completed, CTC will NOT be notified that an SAE is entered.

* See page 61 of the Study Handbook for guidance regarding grade, seriousness, causality and expectedness

If no eCRF accredited site personnel are available, SAEs can be reported using the:

Paper back-up SAE reporting procedure
1) Complete the paper Serious Adverse Event Form
2) Obtain the Investigator’s assessment of the event
3) Email or fax the SAE form (and SAE fax coversheet) to the OUTBACK coordinator to the NHMRC CTC
Follow-up SAE Reports

SAEs are required to be followed up in a timely manner, or as soon as new information becomes available. Even if there is no final outcome yet, when there is any new information, e.g. further diagnosis, outcome, discharge, change to action taken with study treatment etc, a follow-up SAE report is required within 1 working day of the new information.

**TO REPORT AN SAE FOLLOW-UP:**

1) Log into InForm, click on the SAE visit for the relevant patient, and click on the SAE tab

   **DO NOT START A NEW SAE REPORT**

2) Instead, click on the existing SAE report

3) Update any information that has changed

4) When asked for a reason for change, select ‘New Information’

5) Once the SAE is up to date, the Investigator has reviewed the SAE, and the SAE is complete (no yellow fields or red data queries), click ‘Add Entry’ in the Report Details section (item 20) to enter a new row. Enter today’s date, select report type Follow-Up, enter the name of the Investigator who has reviewed the SAE, and enter Yes for ‘Report is complete, authorised and ready for submission’.

An email notification will automatically be sent to the CTC when ‘Report is complete, authorised and ready for submission’ is submitted as Yes in the Report Details row for the Follow-up Report.

**NB:** If a Report Details row is not completed for the Follow-Up Report, CTC will NOT be notified that an SAE follow-up has been entered, i.e. a Report Details row must be entered each time data is entered, added or changed on the SAE.

If clinical recovery is complete at the first follow-up SAE report, no further follow up is necessary. However, if clinical recovery is incomplete, the patient must be followed up until clinical recovery is complete and lab results have returned to normal or disease has stabilised. Follow-up may continue after discharge from hospital or completion of protocol treatment if necessary.
Discharge summaries, extra information and/or copies of test results may be provided separately (i.e. without a follow-up SAE report). Please de-identify all personal information. Please label reports with trial number, date of birth and initials only.

TO RETRACT AN SAE (e.g. an SAE which has been subsequently determined to NOT meet SAE criteria)

1) Log into InForm, click on the SAE visit for the relevant patient, and click on the SAE tab

   **DO NOT START A NEW SAE REPORT**

2) Instead, click on the *existing* SAE report

3) In the Event description, state why the event is not considered to be an SAE.

4) When asked for a reason for change, select ‘New Information’

5) Once the Investigator has reviewed the SAE, click ‘Add Entry’ in the Report Details section (item 20) to **enter a new row**. Enter today’s date, select report type **Retraction**, enter the name of the Investigator who has reviewed the SAE, and enter Yes for ‘Report is complete, authorised and ready for submission’.

   An email notification will automatically be sent to the CTC when ‘Report is complete, authorised and ready for submission’ is submitted as Yes in the Report Details row for the Retraction Report.

   **NB:** If a Report Details row is not completed for the Retraction Report, CTC will NOT be notified that the SAE has been retracted.

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TO FINALISE AN SAE

1) Once all reporting has been completed, i.e. the event has an outcome of recovered or death, the study chair review has been completed, and no further information is expected, the **CTC will contact you** to ask you to finalise the SAE. (Do not perform this step unless requested by the CTC)

2) Log into InForm, click on the SAE visit for the relevant patient, and click on the SAE tab

   **DO NOT START A NEW SAE REPORT**

3) Instead, click on the *existing* SAE report

4) Click ‘Add Entry’ in the Report Details section (item 20) to **enter a new row**. Enter today’s date, select report type **Final**, enter the name of the Investigator who has reviewed the SAE, and enter Yes for ‘Report is complete, authorised and ready for submission’.

   An email notification will automatically be sent to the CTC when ‘Report is complete, authorised and ready for submission’ is submitted as Yes in the Report Details row for the Final Report.

   **NB:** If a Report Details row is not completed for the Final Report, CTC will
Please note the following when completing the SAE form

- **Worst grade**: all events must be graded according to CTCAE version 4.

- **Seriousness**: whether or not the event meets any of the seriousness criteria defined in the protocol.

- **Causality**:
  - Related: there is a reasonable possibility that the intervention / study treatment caused the serious adverse event, i.e. there is evidence to suggest a causal relationship between the intervention / study treatment and the adverse event. This category should be used if the Investigator judges the event is definitely, probably or possibly related to the intervention / study treatment.
  - Unrelated: there is no evidence to suggest a causal relationship between the intervention / study treatment and the adverse event. This category should be used if the Investigator judges the event is unlikely related or not related to the intervention / study treatment.
  - Not Applicable: the event is considered Unrelated to any study treatment.
  - Not received: the patient has never received this intervention / study drug on this trial.

- **Expectedness**:
  - Expected: listed in the investigators brochure, product information or elsewhere in the protocol or patient information sheet.
  - Unexpected: not listed in the investigators brochure, product information or elsewhere in the protocol or patient information sheet.
  - Not Applicable: the patient has never received this intervention / study treatment on this trial.

8.3 GOG and RTOG Reporting Guidelines for CTEP

8.3.1 **Definition of Adverse Events (AE)**

An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease that
occurs in a patient administered a medical treatment, whether the event is considered related or unrelated to the medical treatment.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). The CTCAE v4.0 Manual is also available on the GOG member web site (http://www.gog.org under MANUALS).

8.3.2 Reporting Expedited Adverse Events

Depending on the phase of the study, use of investigational or commercial agents, and role of the pharmaceutical sponsor, an AE report may need to reach multiple destinations. For patients participating on a GOG trial, all expedited AE reports should be submitted by using the CTEP automated system for expedited reporting. All CTEP-AERS submissions are reviewed by GOG before final submission to CTEP. Submitting a report through CTEP-AERS serves as notification to GOG, and satisfies the GOG requirements for expedited AE reporting. All adverse reactions will be immediately directed to the Study Chair for further action.

The requirement for timely reporting of AEs to the study sponsor is specified in the Statement of Investigator, Form FDA-1572. In signing the FDA-1572, the investigator assumes the responsibility for reporting AEs to the NCI. In compliance with FDA regulations, as contained in 21 CFR 312.64, AEs should be reported by the investigator.

8.3.3 Phase 2 and 3 Trials Utilizing a Commercial Agent: CTEP-AERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days of the Last Dose of Any Commercial Study Agent
Reporting Requirements for Adverse Events that occur within 30 Days\(^1\) of the Last Dose of the Commercial Agent on Phase 2 and 3 Trials

<table>
<thead>
<tr>
<th></th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 3</th>
<th>Grades 4 &amp; 5(^2)</th>
<th>Grades 4 &amp; 5(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected and Expected</td>
<td>Unexpected</td>
<td>Expected</td>
<td>Unexpected</td>
<td>With Hospitalization</td>
<td>Without Hospitalization</td>
</tr>
<tr>
<td><strong>Unrelated</strong></td>
<td>Not Required</td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td><strong>Unlikely</strong></td>
<td>Not Required</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>7 Calendar Days</td>
</tr>
<tr>
<td><strong>Possible</strong></td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>24-Hrs; 3 Calendar Days</td>
</tr>
<tr>
<td><strong>Probable</strong></td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>24-Hrs; 3 Calendar Days</td>
</tr>
<tr>
<td><strong>Definite</strong></td>
<td>Not Required</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>7 Calendar Days</td>
<td>Not Required</td>
<td>24-Hrs; 3 Calendar Days</td>
</tr>
</tbody>
</table>

\(^1\) Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with a commercial agent require reporting as follows:

- AdEERS 24-hour notification followed by complete report within 3 calendar days for:
  - Grade 4 and Grade 5 unexpected events
- CTEP-AERS 7 calendar day report:
  - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
  - Grade 5 expected events

\(^2\) Although CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

*Please see exceptions below under the section entitled, “Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent.” March 2005*

*Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.*

- Expedited AE reporting timelines defined:
  - “24 hours; 3 calendar days” – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 3 calendar days of the initial 24-hour report.
  - “7 calendar days” – A complete CTEP-AERS report on the AE must be submitted within 7 calendar days of the investigator learning of the event.

- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported to GOG via CTEP-AERS if the event occurs following treatment with a commercial agent.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.
Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing a Commercial Agent:

- There are no additional instructions or exceptions to CTEP-AERS expedited reporting requirements for this protocol.

### 8.3.4 Procedures for Expedited Adverse Event Reporting:

#### 8.3.4.1 CTEP-AERS Expedited Reports

Expedited reports are to be submitted using CTEP-AERS available at [http://ctep.cancer.gov](http://ctep.cancer.gov). The CTEP, NCI Guidelines: Adverse Event Reporting Requirements for expedited adverse event reporting requirements are also available at this site.

AML/MDS events must be reported via CTEP-AERS (in addition to routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to GOG by telephone at: 215-854-0770. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

#### 8.3.5 Automated CDUS reporting

For studies using commercial agents, the GOG Statistical and Data Center (SDC) routinely reports adverse events electronically to the CTEP Clinical Data Update System (CDUS Version 3.0). The SDC submits this data quarterly. The AEs reported through CTEP-AERS will also be included with the quarterly CDUS data submissions. This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

This study will be monitored by the Abbreviated Clinical Data System (CDUS) Version 3.0.

### 8.4 Safety Reports

The NHMRC CTC will produce regular Safety Reports. These will be sent to GCIG coordinating centers for distribution to all participating investigators, who will in turn inform the local HRECs/IRBs as per local requirements.
9.0 QUALITY ASSURANCE (05/13/2013)

The NHMRC CTC will generate data queries on a regular basis.
The NHMRC CTC will assess timeliness of data submission on a regular basis.
This trial will be monitored by the NHMRC CTC in Australia and New Zealand.
The Gynecologic Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG) will follow the quality assurance procedures set forth by each group.
This trial will be reviewed as part of the NHMRC CTC and ANZGOG’s site audit program. For any site participating in this study, a proportion of patients from this trial may be selected for source data verification and review of regulatory files and pharmacy records. The investigator, by agreeing to participate in this protocol, agrees to cooperate fully with any quality assurance visit undertaken by third parties, including representatives of ANZGOG, national and/or foreign regulatory authorities as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, patient hospital charts, other source documents and other study files) to these individuals.

9.1 Radiotherapy (RT) quality assurance (QA) (05/13/2013)

Radiotherapy quality control (RT QA) is provided by the IROC Houston QA Center (formerly Radiological Physics Center) in Houston TX, USA.

Please view the IROC website at [http://rpc.mdanderson.org](http://rpc.mdanderson.org)

There is a link to the OUTBACK trial on the main webpage. The OUTBACK page explains the steps involved in the QA process and lists the documents that need to be submitted.

The current protocol specifies the requirements and frequency for RT auditing.

### External beam radiation therapy

Please submit to the RPC: 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](http://rpc.mdanderson.org) under Forms).

### Brachytherapy

Please submit to the RPC: Simulator films, digitally reconstructed radiographs (DRRs) CTs, MRIs or US 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](http://rpc.mdanderson.org) under Forms).
10.0 TRIAL INSURANCE

The OUTBACK trial is an investigator-initiated collaborative group study for which there is no industry sponsor designated to provide indemnity.

Therefore each participating centre must provide its own indemnity for the study.

Trial insurance is not required for sites in the United States. For GOG sites outside of the United States, trial insurance may be required and should be paid out of the sites’ GOG funds.

For RTOG sites, each participating centre must provide its own indemnity for the study.

11.0 SITE PAYMENTS

Payments will be made to GOG sites using the standard method for membership, per capita and translational research point reimbursement currently employed by GOG.

GOG point reimbursement for GOG sites is as follows:

Membership-6

Per Capita- 20

TR Per Capita- Award based on specimen submissions. Distribution: 1.0 point for a block or 15 unstained slides of formalin-fixed and paraffin-embedded (FFPE) tumor including primary and/or metastatic tumor that is available from a previous surgery or biopsy, 0.5 point for a frozen blood specimen, and 0.5 point for each of three plasma specimens up to a maximum of 4 points.

Payments will be made to RTOG sites using the standard method for membership.