

Statistical Analysis Plan

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Abbreviations and Definitions

Abbreviations	Definitions
AE	Adverse event
AUC	Area under the curve
CR	Complete response
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
ECOG	Eastern cooperative oncology group
EDTA	Ethylenediaminetetraacetic acid
FAS	Full analysis set
FDG	Fluorodeoxyglucose
K-M	Kaplan-Meier
MedDRA	Medical dictionary for regulatory activities
NCI	National cancer institute
PET	Positron emission tomography
PFS	Progression-free survival
PID	Percentage intended dose
PR	Partial response
RDI	Relative dose intensity
SAE	Serious adverse event
SS	Safety set

1 Introduction

1.1 Preface

Metastatic seminoma is a relatively infrequent disease entity. The conventional treatment for it, namely cisplatin and etoposide with or without bleomycin, has a progression-free survival (PFS) rate at 3 years of over 81% compared to 71% treated with carboplatin area under the curve (AUC) 7 [1]. Several studies have addressed the use of single agent carboplatin in metastatic seminoma. Studies have generally concluded that although PFS is inferior to that seen with cisplatin based therapy, as a large number of relapsing patients could be salvaged, the overall survival was unchanged and indeed toxicity was substantially reduced [1, 2].

The Orchid Clinical Trials Group recently completed a study in metastatic seminoma using carboplatin AUC-10. Twenty patients received this dose of carboplatin for metastatic seminoma, with a median follow up of 29.4 months. Following the closure of the study a further 20 patients have received carboplatin AUC-10. In total 40 patients have been treated. There have been 2 relapses to date (5%), compared to the 18% relapse seen within the first 2 years of treatment of 28 patients who received AUC 7 or less with a median follow up of 135 months. The relapsed patients were successfully salvaged using conventional chemotherapy. As nearly all relapses occur within 2 years of therapy, a 2 year PFS is an appropriate endpoint for this phase II study.

In this most recent study, the protocol stipulated that all patients who were not in complete remission by day 21 of the first cycle would receive 4 rather than 3 cycles. This led to all those who essentially had greater than 2B disease requiring 4 cycles. This was probably unnecessary as most patients achieved a complete response (CR) eventually – it just took time for the masses to shrink.

It is hoped, in the Car-PET study, that by substituting conventional computed tomography (CT) for positron emission tomography (PET) CT a greater proportion of patients will achieve a complete metabolic response and therefore the 4th cycle may be avoided in more patients. This will allow shortening of the treatment and reduction in the use of blood products as most of the blood transfusions required occur during the 4th cycle of carboplatin.

1.2 Purpose of the Analyses

These analyses will assess the safety, efficacy and toxicity of carboplatin AUC-10 in metastatic seminoma in a multi-centre setting. The aim is to see if, by using Fluorodeoxyglucose (FDG) PET-CT to assess metabolic response, the number of patients requiring 4 cycles can be reduced.

2 Study Objectives and Endpoints

Primary Objective	Endpoints
2-year PFS rate	<p>PFS rate for carboplatin AUC-10 at 2 years measured from the date of study enrolment to the date of disease progression or death.</p> <p>The study result will be considered positive if the PFS rate for patients on carboplatin AUC-10 is consistent with a true difference of 15% or more from standard chemo i.e. if there are at least 39 PFS patients out of the first 45 patients at 2 years.</p>
Secondary Objectives	Endpoints

Metabolic response rate	Proportion of patients meeting each of the response categories as defined in Appendix 2 of the protocol.
Overall response	Overall response at the end of the treatment
Overall survival	Median overall survival time measured from the date of study enrolment to the date of death.
Toxicity level	Percentage of adverse events (grade 3 or 4 according to CTCAE version 4.03 criteria) in terms of treatment cycle of any type (including vomiting, nausea and diarrhoea).

3 Study Methods

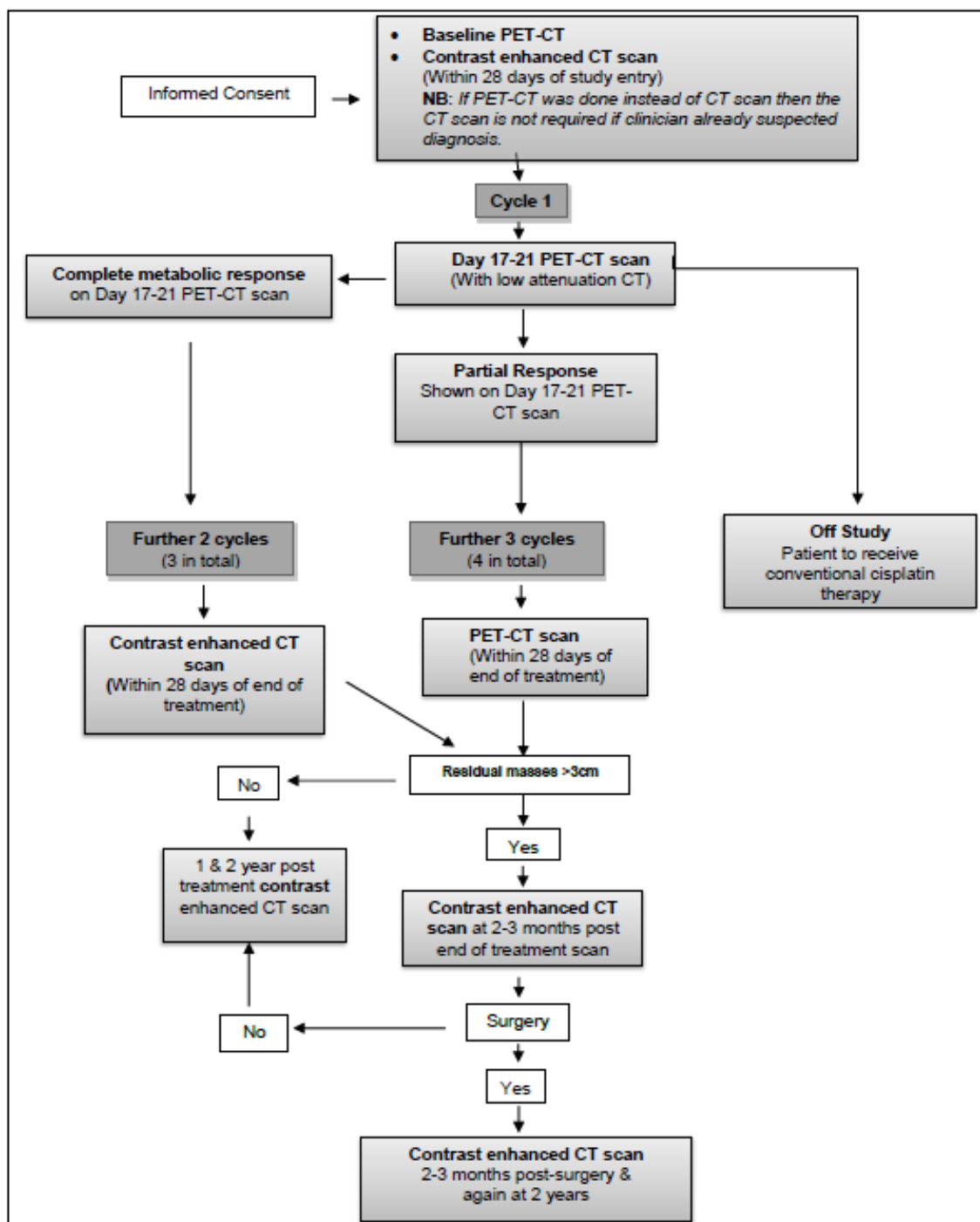
3.1 General Study Design and Plan

This is a single arm phase II study to assess the safety, efficacy and toxicity of carboplatin AUC-10 in metastatic seminoma. Up to 50 patients will be recruited into the study over four years (assuming 5 patients may drop out for reasons other than disease progression/intolerable side effects). 45 evaluable patients will be necessary to establish activity of carboplatin AUC10 in this setting. Patients will be recruited for 48 months. Patients will be followed up as part of the study for 2 years following completion of treatment. The end of the study will be 3 months after the date when the last patient has completed his final follow up visit.

Prior to the commencement of treatment, the patient should have a baseline PET-CT scan and a contrast enhanced CT scan performed within 28 days of study entry. Patients will be treated with carboplatin AUC-10 every 3 weeks (3 weeks=1 cycle) and on day 17-21 of the first cycle a repeat PET-CT scan will be performed. If the patient has a complete metabolic response (see Appendix 3 of the protocol), a further 2 cycles of carboplatin will be given, leading to a total of 3, and if the patient has not had a complete metabolic response but is responding, a further 3 cycles of carboplatin will be given.

If a patient is showing no response to treatment then the patient will be taken off study and will receive conventional therapy using a cisplatin-based combination.

Figure 1: Treatment Flowchart



3.2 Inclusion-Exclusion Criteria and General Study Population

3.2.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Metastatic seminoma – International Germ Cell Cancer Collaborative Group (IGCCCG) good prognosis.
2. Glomerular filtration rate of over 25 ml/min (creatinine clearance should preferably be assessed using an ethylenediaminetetraacetic acid [EDTA] clearance).
3. Eastern cooperative oncology group (ECOG) performance status 0-3.
4. Normal Alpha-fetoprotein (All levels of Human chorionic gonadotropin and lactate dehydrogenase are acceptable).
5. Males aged greater than 18 and less than 75 years.
6. Able to give written informed consent prior to study entry.
7. Patients must be sterile or agree to use adequate contraception during the period of therapy.

3.2.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Metastatic seminoma with any non-pulmonary visceral metastases.
2. Raised Alpha-fetoprotein.
3. Any previous chemotherapy or radiotherapy.
4. Currently enrolled in any other investigational drug study.
5. Other malignancy except basal cell.

3.3 Randomisation and Blinding

This is an open-label single arm phase II study therefore randomisation and blinding are not applicable.

3.4 Study Variables

3.4.1 Primary and Secondary Variables

3.4.1.1 Primary Efficacy Variables

3.4.1.1.1. Progression-Free Survival (PFS)

PFS is defined as the time between the date of enrolment to first evidence of disease progression based on central review or death, whichever occurs first. For patients who have not died or experienced disease progression at the end of study, PFS will be censored on the last date the patient was known to be progression-free. Patients with no post-baseline tumour assessment will be censored at the date of enrolment plus 1 day. The PFS time will always be derived based on scan/assessment dates not visit dates.

3.4.1.2 Secondary Efficacy Variables

3.4.1.2.1. Metabolic Response Rate

One of the aims of this study is to see if, by using FDG PET-CT to assess metabolic response, the number of patients requiring 4 cycles can be reduced. There are currently no well validated metabolic response criteria for PET-CT in seminoma. Hence, we will use the criteria for the assessment of response developed for the evaluation of lymphoma (see Appendix 2 in the protocol).

3.4.1.2.2. Overall Survival

Overall survival is defined as the time from date of enrolment to the date of death due to any cause. All deaths will be included, whether they occur on study treatment or following treatment discontinuation. For patients who have not died, OS will be censored at the date of last contact. Methods for handling censoring and for analysis are the same as those described for PFS.

4 Sample Size

The primary objective is to gain a preliminary indication on whether carboplatin AUC-10 is worthwhile considering in a phase III study, using the PFS rate as a criterion. A'Hern's single-stage procedure is used to estimate the number of patients required [3].

The primary outcome is the percentage of patients progression-free at 2-years. Therefore, all patients must have at least 2-years follow-up (unless they have died or their disease has progressed). A Medical Research Council (MRC) study [1] showed that PFS rate at 3 years in standard chemotherapy, bleomycin, etoposide, cisplatin (BEP), is 81%. It is also known that PFS rate at 2-years and 3-years are the same [2]. Carboplatin AUC-10 should not therefore have a 2-year PFS rate of 75% or less, and it would only be worth considering in a phase III study if the true rate were 90% or more. This information is used in A'Hern's single stage design to yield a sample size of 45 patients, with 80% power and one-sided test of significance at the 5% level. Here the statistical assumption of this design is that there is 80% chance of concluding that carboplatin AUC-10 is effective if the true response rate is 90% or more, but only a 5% chance of concluding it is effective if the response rate is 75% or less. To allow for a 10% drop-out rate the intention is to recruit up to 50 patients.

5 General Considerations

5.1 Timing of Analyses

The data will be analysed at the end of the study. No formal interim analyses are planned as the carboplatin AUC-10 is considered to be relatively safer than the standard chemotherapy. However, analysis may be performed for conference presentations after all patients have been recruited and treated, but have not completed the follow-up time. This may only be done after recruitment of all patients and completion of treatment and hence unlikely to affect the study.

5.2 Analysis Sets

5.2.1 Definition of Analysis Sets

Two analysis sets will be defined:

5.2.1.1 Full Analysis Set (FAS) population

The FAS will consist of all patients who completed at least one cycle of carboplatin AUC-10 and for whom relevant data is available at baseline and follow up. All efficacy analyses will be performed on the FAS population.

5.2.1.2 Safety Set (SS) population

The SS will consist of all patients who meet the eligibility criteria and received at least one dose (cycle) of carboplatin AUC-10. Patients who did not receive any doses of study treatment will be excluded from the safety population. All safety analysis will be performed on the SS population.

5.2.2 Protocol Deviations

All-important deviations related to study inclusion or exclusion criteria, conduct of the trial, subject managements or subject assessment will be tabulated and listed.

5.3 Missing Data

No imputation will be performed for missing data as it is a single arm study. Data that are potentially spurious or erroneous will be examined under the auspices of standard data management operating procedures.

5.4 Interim Analyses and Data Monitoring

There are no planned independent data monitoring committee (IDMC) reviews as the Carboplatin AUC-10 is considered to be relatively safer than the standard chemotherapy. However, the interim data is analysed for conference presentation.

5.5 Multi-centre Studies

This is a phase II multicentre trial. It is not expected that centre will have any effect to the primary outcomes.

5.6 Multiple Testing

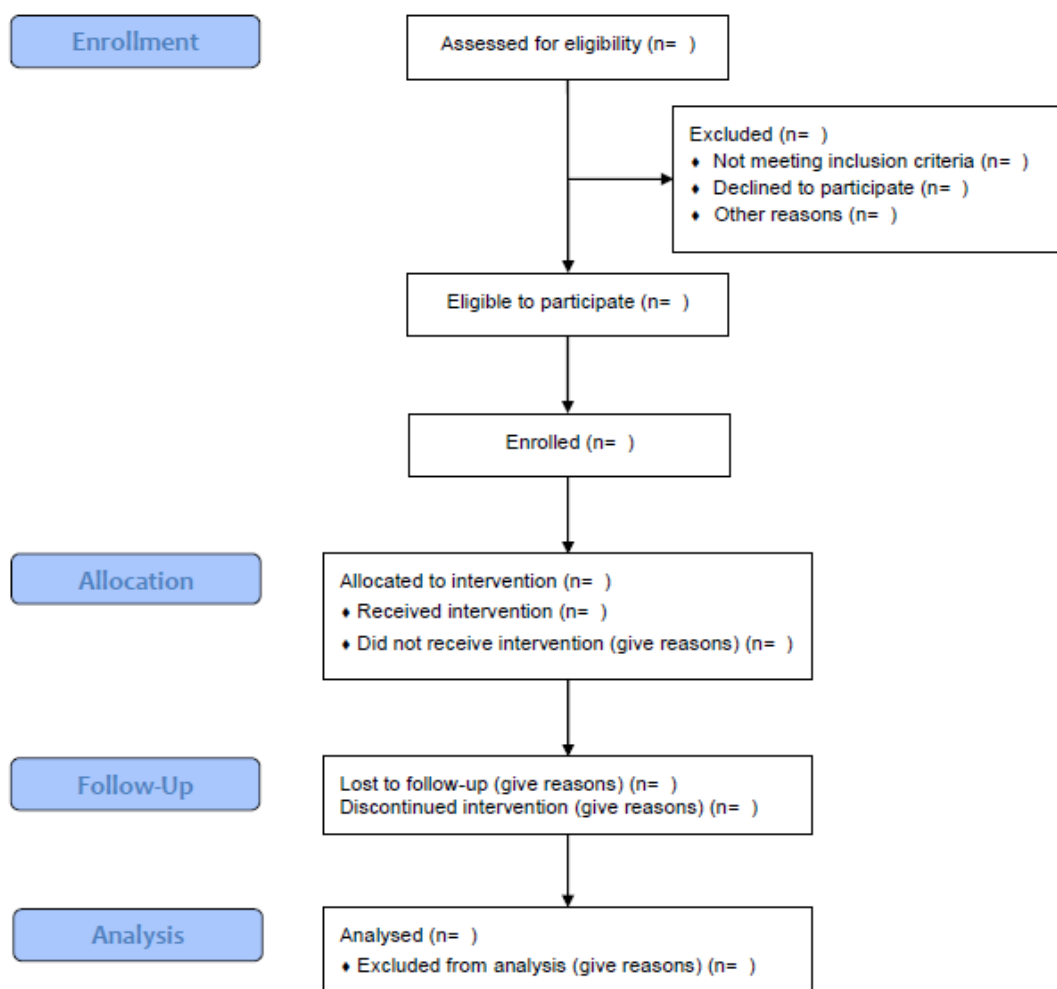
No adjustment for multiple comparison will be performed.

6 Summary of Study Data

Study data will be summarised using appropriate summary statistics (i.e. mean, standard deviation, median, and range for continuous variables, and number and proportion of patients for categorical variables). Summaries will be presented for the SS population. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

6.1 Subject Disposition

A CONSORT diagram will be produced as follows (as applicable):



The number of patients enrolled will be tabulated by study site. Patient disposition will be tabulated, and reasons for premature discontinuation will be summarised.

6.2 Demographic and Baseline Variables

Demographic and baseline characteristics (age; primary location; stage; ECOG PS; Tumour markers; BHCG; LDH; EDTA or measured creatinine clearance will be summarised.

6.3 Concurrent Illnesses and Medical Conditions

All AEs and serious AEs (SAEs) will be coded according to the latest available Medical Dictionary for Regulatory Activities (MedDRA) version. The Chief Investigator may wish to group MedDRA codes further into more clinically meaningful groups for analysis and interpretation. Any grouping of toxicity codes will be signed off by the Chief Investigator.

6.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarised in terms of frequency. Medication will be coded using Systematized Nomenclature of Medicine (SNOMED).

6.5 Treatment Compliance

Treatment compliance will be presented for all patients in the SS in terms of:

- Median and range for each cycle length.
- Frequency and percentage of patients having a dose reduction.

- Frequency and percentage of patients having a dose reduction due to low platelet count (<20).
- Frequency and percentage of patients discontinuing investigational medicinal product (IMP).
- Frequency and percentage of patients leaving the study due to disease progression or death.

7 Efficacy Analysis

7.1 General Principles

Efficacy data will be summarised using appropriate summary statistics (i.e. mean, standard deviation, median, and range for continuous variables, and number and proportion of patients for categorical variables). CIs will be calculated as appropriate. Summaries will be presented for the FAS population. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

7.2 Primary Efficacy Analysis

7.2.1 PFS

Kaplan-Meier (K-M) methodology will be used to estimate the median PFS. The median PFS and PFS rate for carboplatin AUC-10 at 2-years will be estimated with one-sided 95% CI to be consistent with one-sided test. However, 2-sided 95% CI will also be presented. The study result will be considered positive if the PFS rate for patients on carboplatin AUC-10 is consistent with a true difference of 15% or more from standard chemo i.e. if there are at least 39 PFS patients out of the first 45 patients at 2 years.

7.3 Secondary Efficacy Analysis

7.3.1 Metabolic Response Rate

The number and percentage of subjects falling into each response category defined in Appendix 2 of the protocol i.e. the categories of: CR, PR marker positive, PR marker negative, stable disease, and progressive disease after one cycle will be descriptively tabulated.

7.3.2 Overall response

Overall treatment responses will be measured using the same criteria described in our previous phase II study 5, which are consistent with other published reports. Progressive disease is defined as the development of new sites of disease with rising tumour markers if present. Stable disease is defined as the lack of any new sites of disease and a <90% reduction in tumour markers, 28 days after chemotherapy. Marker-positive partial response (M+ve PR) is defined as a >90% reduction in tumour markers (without normalisation) for ≥28 days, and no new sites of disease. Marker-negative PR (M-ve PR) is defined as a normalisation of tumour markers and no new sites of disease for ≥28 days. For those patients who have normal tumour markers before chemotherapy, a M-ve PR required a 50% reduction in the bi-dimensional measurements of the residual masses to be maintained for ≥28 days. Complete remission (CR) is defined as a normalisation of tumour markers with a complete resolution of all sites of disease. Postsurgical outcome is defined as outcome after surgery performed to remove all sites of disease, and patients who achieves a radiological CR to chemotherapy alone or has a surgically induced CR is deemed to have no evidence of disease (NED).

7.3.3 Overall Survival

Analysis methods are the same as those described for PFS in Section 7.2.1.

8 Safety Analysis

Safety data will be summarised using appropriate summary statistics (i.e. mean, standard deviation, median, and range for continuous variables, and number and proportion of patients for categorical variables). Summaries will be presented for the SS population. The baseline value of any variable will be defined as the last available value prior to the first administration of study treatment.

8.1 Extent of Exposure

Sometimes the doses are recalculated on Aria - prescribing system if there has been a change in creatinine- these lead to minor changes and hence they are not counted as dose-reduction as they are all less than 10%. Exposure data will be summarised, indicating total exposure to study drug, as well as the number of any dose reductions.

8.2 Adverse Events (AEs)

AEs, irrespective of relatedness, will be summarised. Verbatim descriptions of treatment-emergent AEs will be mapped to the appropriate thesaurus terms and summarised by mapped MedDRA term, and national cancer institute (NCI) CTCAE grade. For each patient's AE, the maximum severity reported will be used in the summaries. SAEs, including deaths, will be summarised separately. Specifically, the following descriptive statistics will be generated.

1. Incidence of SAEs.
2. Incidence of grade 3 and 4 AEs (CTCAE, version 4.03).
3. Incidence of all AEs of all grades.

8.3 Deaths, Serious Adverse Events (SAEs) and other Significant Events

All deaths, SAEs and other significant events will be summarised in line listings. SAEs will be reconciled with the AEs.

8.4 Clinical Laboratory Evaluations

Laboratory data will be tabulated, with values outside normal ranges identified and summarised by NCI CTCAE (Version 4.03) grade. Barts Normal ranges will be used as reference. The worst condition for each patient during the entire treatment will be reported.

8.5 Other Safety Measures

8.5.1 Vital Signs

Changes in vital signs data (if applicable) will be summarised by scheduled measurement time. Vital signs will include height (cm), weight (kg), temperature (degrees Celsius), blood pressure, respiratory rate, and heart rate.

ECOG performance score will also be summarised by scheduled time point.

9 Reporting Conventions

The mean, standard deviation, and any other statistics other than quantiles, will be reported to one decimal place greater than the original data. Quantiles, such as median, or minimum and maximum will use the same number of decimal places as the original data.

10 Technical Details

Analysis will be conducted using Stata v 13 (or subsequent versions). A second statistician will independently double check the statistical codes for the main endpoints of analysis following our Statistical standard operation procedure (SOP).

This SAP is based on Car-PET Protocol: Master Version 8.0 dated 31st August 2017. All programs will be stored in the *G:\Experimental Cancer Medicine\Statistics\Inhouse Unblinded\Car-PET* folder until the end of the study at which point they will be merged with the trial master file (TMF) for archiving.

11 Summary of Changes to the Protocol

12 References

1. Horwich A, Oliver RT, Wilkinson PM, et al.: A medical research council randomized trial of single agent carboplatin versus etoposide and cisplatin for advanced metastatic seminoma. MRC Testicular Tumour Working Party. British Journal of Cancer 2000; 83(12): 1623-9.
2. Bokemeyer C, Kollmannsberger C, Stenning SP, et al.: Metastatic seminoma treated with either single agent carboplatin or cisplatin-based combination chemotherapy: a pooled analysis of two randomised trials. Br J Cancer 2004; 91(4): 683-687.
3. A'Hern RP: Sample size tables for exact single-stage phase II designs. Stat Med 2001; 20(6): 859-66.