RATHL TRIAL

A Randomised Phase III Trial to Assess Response Adapted Therapy Using FDG-PET Imaging in patients with Newly Diagnosed, Advanced Hodgkin Lymphoma

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Name & Role:	Signature:	Date authorised:
Chief Investigator: Professor Peter Johnson Medical Oncologist		30 October 2013
For the Sponsor Professor Jonathan Ledermann Director, UCL CTC		12 Nov 2013
Paul Smith Tumour Group Lead, UCL CTC		18/11/2013

Please note: This trial protocol must not be applied to patients treated outside the RATHL trial. UCL CTC can only ensure that approved trial investigators are provided with amendments to the protocol.

Coordinating Centre:

For general queries, supply of trial documentation and central data management please contact:

RATHL Trial Coordinator
Cancer Research UK & UCL Cancer Trials Centre
90 Tottenham Court Road
London
W1T 4TJ

Tel: +44 (0) 20 7679 9860
Fax: +44 (0) 20 7679 9861
09:00 to 17:00 Monday to Friday (UK time)
Email: rathl@ctc.ucl.ac.uk

Other trial contacts:

Chief Investigator: Professor Peter Johnson
Address: Southampton General Hospital
Cancer Research UK Clinical Centre
Somers Cancer Research Building
Southampton
SO16 6YD

Trial Management Group (TMG):

UK		
Professor Peter Johnson	Consultant Medical Oncologist	Southampton General Hospital
Dr Sally Barrington	Consultant Physician	Guy's and St Thomas' Hospital
Dr Cathy Burton	Consultant Haematologist	St James's University Hospital
Professor John Radford	Consultant Medical Oncologist	Christie Hospital
Amy Kirkwood	Statistician	UCL CTC
Paul Smith	Tumour Group Lead	UCL CTC
Lindsey Stevens	Trial Coordinator	UCL CTC
Thomas Roberts	Trial Coordinator	UCL CTC
Rumana Jalil	Data Manager	UCL CTC
Overseas		
Dr Leanne Berkahn	Consultant Haematologist	ALLG, New Zealand
Dr Gunilla Enblad	Consultant Oncologist	Uppsala University Hospital, Sweden
Dr Alexander Fossa	Consultant Medical Oncologist & Radiotherapist	Norwegian Radium Hospital
Dr Francesco d'Amore	Chief Physician	Aarhus University Hospital
Dr Stefano Luminari	Consultant Oncologist	GISL, Italy
Prof Massimo Federico	Consultant Medical Oncologist	Modena, Italy
Dr Judith Trotman	Consultant Haematologist	ALLG, Australia
Dr Brian Hennessy	Consultant Haematologist	St James Hospital, Ireland

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1.0 PROTOCOL SUMMARY

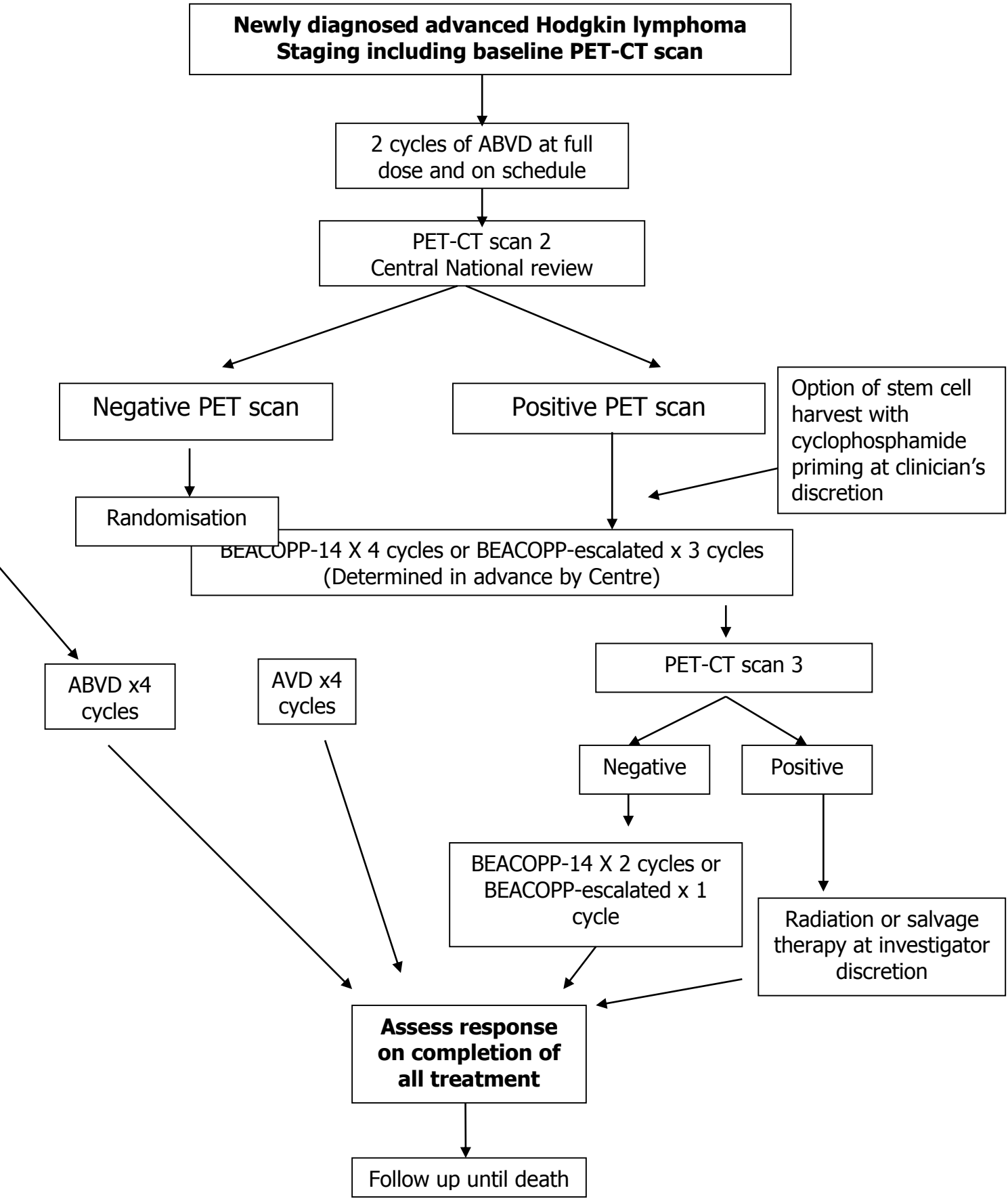
1.1 Study Synopsis

Study Title	A Randomised Phase III Trial to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin Lymphoma
Short study title	PET for response adapted therapy in advanced Hodgkin Lymphoma (RATHL)
Start and end dates of study	Start date: May 2008 Patients will be recruited over 3-4 years and followed until death
Primary outcome measure	3 year progression-free survival
Secondary outcome measures	Overall survival, toxicity, both acute (during the treatment) and long-term until 5 years from randomisation
Clinical Phase	Phase III
Study design	A multi-centre randomised trial comparing treatment outcome for patients with advanced Hodgkin lymphoma, using FDG-PET imaging after 2 cycles of ABVD to determine response and subsequent management
Number of patients	1200 patients in total
Eligibility criteria (see protocol section 5.3)	**Inclusion Criteria** • Histologically confirmed classical Hodgkin lymphoma according to the WHO classification • Aged 18 or over • Stage IIB-IV or stage IIA with adverse features • No previous chemotherapy, radiotherapy or investigational drug for HL • Performance status 0-3 • Adequate bone marrow function (platelets $>100x10^9$/l, neutrophils $>1.5x10^9$/l unless due to bone marrow infiltration with lymphoma • Creatinine <150% of ULN; bilirubin <2 x ULN; transaminases <2.5 x ULN • Patients with a significant history of ischaemic heart disease or hypertension must have acceptable left ventricular ejection fraction (≥50%) • Life expectancy > 3 months • Patients of childbearing potential must be willing to use adequate contraceptive precautions • Written informed consent • Access to an approved PET scanner **Exclusion criteria** • Poorly controlled diabetes mellitus • Other concurrent uncontrolled medical condition • Pregnant or lactating • Known CNS or meningeal involvement by lymphoma • Cardiac contraindication to doxorubicin • Neurological contraindication to chemotherapy • General status that does not allow the administration of a full course of chemotherapy • Concurrent active malignancy within the past 5 years, except non-melanoma skin cancer or squamous cell carcinoma of the cervix. • Known positive serology for HIV, hepatitis B or hepatitis C Medical or psychiatric conditions that compromise the patient's ability to give informed consent

<table>
<tr><td>Initial treatment for 2 cycles
(see protocol section 7.2)</td><td>ABVD (cycle repeats every 28 days)
Doxorubicin 25mg/m^2 iv Days 1 & 15
Bleomycin 10,000 iu/m^2 iv Days 1 & 15
Vinblastine 6mg/m^2 iv Days 1 & 15
Dacarbazine 375mg/m^2 iv Days 1 & 15

This will be given at full dose and on schedule, regardless of blood count. Growth factors may be used at the discretion of investigators but are not routinely advised.</td></tr>
<tr><td>After 2 cycles, PET negative patients randomised to ABVD or AVD (for 4 cycles)
(see protocol section 7.2)</td><td>ABVD as above, every 28 days for further 4 cycles
or
AVD every 28 days for further 4 cycles
Doxorubicin 25 mg/m^2 iv Days 1 & 15
Vinblastine 6 mg/m^2 iv Days 1 & 15
Dacarbazine 375 mg/m^2 iv Days 1 & 15</td></tr>
<tr><td rowspan="2">After 2 cycles, PET positive patients will receive either BEACOPP-14 (for further 4-6 cycles) or BEACOPP escalated (for 3-4 cycles) (specified in advance by centre)
(see protocol section 7.2)</td><td>BEACOPP-14 for 4-6 cycles (Cycle repeats every 14 days)
Doxorubicin 25 mg/m^2 iv Day1
Cyclophosphamide 650 mg/m^2 iv Day 1
Etoposide 100 mg/m^2 iv Days 1-3
Procarbazine 100 mg/m^2 po Days 1-7
Prednisolone 80 mg/m^2 po Days 1-7
Bleomycin 10,000 iu/m^2 iv Day 8
Vincristine* 1.4 mg/m^2 iv Day 8
* maximum 2mg
G-CSF 263/300 mcg s/c Days 9-13
(or PEG-filgrastim single dose)</td></tr>
<tr><td>BEACOPP-escalated for 3-4 cycles (Cycle repeats every 21 days)
Doxorubicin 35 mg/m^2 iv Day1
Cyclophosphamide 1250 mg/m^2 iv Day 1
Etoposide 200 mg/m^2 iv Days 1-3
Procarbazine 100 mg/m^2 po Days 1-7
Prednisolone 40 mg/m^2 po Days 1-14
Bleomycin 10,000 iu/m^2 iv Day 8
Vincristine* 1.4 mg/m^2 iv Day 8
* maximum 2mg
G-CSF 263/300 mcg s/c Days 9-13
(or PEG-filgrastim single dose)</td></tr>
<tr><td>Radiotherapy</td><td>PET negative patients will not receive radiotherapy as part of their initial therapy. PET positive patients may receive radiotherapy to sites of FDG uptake at the completion of chemotherapy, although it is anticipated that patients who become PET negative and who are in radiological complete remission will not receive radiotherapy</td></tr>
<tr><td>Treatment duration</td><td>Approx 6-8 months</td></tr>
<tr><td>Timing of trial PET scans
(see sections 5.1, 8.2.1 & 8.2.2)</td><td>Baseline (all patients):
• Before starting treatment; no more than 28 days before trial registration
Post cycle 2 (all patients):
• 9-13 days after cycle 2 day 15
BEACOPP interim PET scan (PET positive patients only):
• BEACOPP-14: between days 10-14 of cycle 4
• Escalated BEACOPP: between days 17-21 of cycle 3
All scans must be performed at an approved centre, on the same scanner and in accordance with the trial scanning protocol (appendix 5)</td></tr>
</table>

1.2 Trial Outline



2.0: INTRODUCTION

2.1 Disease Background

Hodgkin lymphoma accounts for approximately 15% of all lymphomas. The age-adjusted annual incidence of Hodgkin lymphoma is approximately 2.7 per 100,000. More than 90% of cases occur in adults, ranging in age from 16 years upwards with a median age of presentation of approximately 35 years[1].

Hodgkin lymphoma is highly sensitive to chemotherapy or radiation therapy and long-term cure rates of greater than 80% are achieved even in patients with advanced disease[2]. However there remains a subgroup of patients with disease which responds poorly or fails to respond to initial therapy[3]. Although prognosis at diagnosis can be estimated using established and validated pre-treatment prognostic indices[4], response to treatment is probably the most important single prognostic factor for the individual patient. Accordingly, it is desirable to identify these patients as early as possible during treatment so that risk-adapted individually-tailored treatment can be administered, aiming to lower the risk of treatment failure, avoid unnecessary toxicity for those in the best prognosis group and increase the probability of long-term survival. Risk-adapted therapy, aiming to achieve high cure rates with minimal long-term morbidity and mortality, requires reliable prognostic stratification. PET (positron emission tomography) imaging has a number of potential advantages in refining and improving the management of patients with Hodgkin lymphoma. By using PET imaging it should be possible to identify those patients in whom initial therapy is ineffective, initiating an earlier switch to more intensive treatment. This should reduce the magnitude of treatment related morbidity and mortality and ultimately improve cure rates.

2.2 The use of PET in Hodgkin lymphoma

PET scanning has been used in Hodgkin lymphoma at diagnosis for staging, during treatment to assess response and to evaluate residual masses and after completion of treatment for prediction of relapse[5]. 2-(18F)fluoro-2-deoxy-D-glucose (FDG) PET is a functional imaging technique, which relies on the detection of a higher rate of glucose metabolism in malignant cells compared with normal cells. Conventional radiological methods, eg CT scanning, have significant limitations in assessing response to therapy. A reduction in tumour size is used as the most important determinant, but this is not an accurate predictor of outcome as the malignant cells in Hodgkin lymphoma, often make up only a small proportion of the tumour volume, and it takes time for a reduction in tumour size to occur and thus this cannot be used as a basis for response assessment and therapy adjustment until late during treatment. FDG-PET allows evaluation of metabolic rather than morphological or volume changes, allowing earlier assessment of tumour response during therapy.

Several studies have assessed the role of PET imaging in response assessment in HL. Friedberg et al reported a study of 22 patients with de novo HL who were imaged by FDG-PET after 3 cycles of chemotherapy[6]. After a median follow-up of 2 years, 4 out of 5 interim PET positive patients had progressed and 15 of 17 PET negative patients remained in remission. Hutchings et al, retrospectively assessed the prognostic value of early interim

PET in 85 patients with HL[7]. At a median follow-up of more than 3 years, PET imaging had a strong positive predictive value in advanced HL, independent of the other known prognostic factors. In a further study, the same group studied 77 newly diagnosed patients with HL, who underwent FDG-PET at staging, after 2 and 4 cycles of chemotherapy, and after completion of chemotherapy[8]. After 2 cycles of chemotherapy, 61 patients had a negative PET scan and 16 patients a positive one. At median 2 year follow up, 11 of 16 PET positive patients had progressive lymphoma and 2 died. Three of 61 PET negative patients had recurrences, although all remained alive. In this study there was a strong association between early PET after 2 cycles and progression-free (PFS) and overall survival. For prediction of PFS, interim FDG-PET was as accurate after 2 cycles as later during treatment and superior to CT at all times. In regression analyses, early interim FDG-PET was stronger than established baseline prognostic factors. Similarly, an Italian group reported the results of PET imaging after 2 cycles of ABVD[9]. The scan was positive in 20 patients, of whom 17 progressed during therapy, one relapsed and two remained in CR. By contrast, 85/88 (97%) patients with a negative scan remained in CR. These studies suggest that early PET is predictive of complete response and particularly highlight that interim assessment of response by PET imaging is superior to assessment after completion of treatment for prediction of disease progression, with a very low false-negative rate. Collective data from the Italian and Danish groups prospectively evaluated and compared the prognostic role of FDG-PET and the International Prognostic Score (IPS) in 260 newly diagnosed patients with advanced HL, treated with conventional ABVD and consolidation radiotherapy if indicated. FDG-PET scan was performed at baseline and after two courses of ABVD, with no treatment change allowed on the basis of the PET-2 results. After a median follow-up of 2.19 years (range, 0.32 to 5.18 years), 205 patients were in continued complete remission, 2 patients were in partial remission, 43 patients progressed during therapy or immediately after and 10 patients had relapsed. The 2-year PFS for patients with positive PET-2 results was 12.8% and for patients with negative PET-2 results was 95% ($P < .0001$). In multivariate analyses, only PET-2 results were significant ($P < .0001$). Therefore this trial showed that PET-2 has better prognostic value than IPS and emerges as the single most important tool for planning of risk-adapted treatment in advanced HL[10]. Thus, PET is a strong and independent predictor of PFS and allows early identification of those patients with a suboptimal response to initial therapy. The results of continued treatment with ABVD in the group remaining PET-positive after 2 cycles are extremely poor, justifying an early switch to more intensive treatment in the hope of salvage.

One of the issues around PET scanning that has been little addressed in the publications to date is that of reproducibility. There is recognition that the interpretation of FDG-PET scans is an evolving field with person-to-person and centre-to-centre variation. One particular advantage of conducting a large collaborative study is the opportunity to develop a standardised approach to the reporting of PET scan results, validated by using them to guide subsequent therapy. This is one of the important secondary goals of this trial.

2.3 Study Drugs Background

The chemotherapy regimen ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) given every 14 days was established from clinical trials in the late 1990s to result in the highest efficacy with reduced toxicity in advanced Hodgkin lymphoma and is considered the standard of care for all patients[11]. In order to improve cytotoxic delivery without

compromising benefit, other multiagent chemotherapy regimens have been developed, but none has clearly demonstrated a survival advantage over ABVD[12]. Several groups have placed emphasis on developing novel, brief duration regimens for the treatment of advanced Hodgkin lymphoma. The rationale behind the development of these regimens is to increase dose-intensity of chemotherapy by reduction in the total duration of treatment (based on retrospective analyses suggesting a relationship between treatment outcome and dose intensity), reducing cumulative doses of several drugs thought to be responsible for long term toxic effects, including alkylating agents, doxorubicin and bleomycin, and reducing the extent of radiation therapy, with an anticipated further reduction in cardiac and pulmonary toxicity. Such alternative treatment regimens include Stanford V[13] and BEACOPP[14]. Autologous transplantation has been reserved for those patients failing to achieve complete remission with initial chemotherapy or who have subsequently relapsed[15-17].

The BEACOPP regimen devised by the German Hodgkin Lymphoma Study Group (GHSG) substitutes etoposide for dacarbazine and vinblastine and encompasses two main intensification principles: dose escalation of the putative most important drugs (cyclophosphamide, etoposide, and doxorubicin) and time intensification accomplished by shortening the respective chemotherapy cycles from 4 to 3 weeks. Two different variants of BEACOPP were initially designed: BEACOPP in baseline dosage (BEACOPP-21) and BEACOPP in escalated dosage with granulocyte colony-stimulating factor (G-CSF) support (BEACOPP-escalated). Within the randomized multicentre HD9 trial, it was demonstrated that the BEACOPP variants led to a significantly lower progression rate and an improved failure-free and overall survival as compared with standard COPP/ABVD[14]. At 34 months, freedom from treatment failure (FFTF) rates were 90% and 81% for BEACOPP-escalated and BEACOPP-21 respectively. Whilst BEACOPP-escalated may result in better treatment outcomes, it remains to be determined whether the increased toxicity of this regimen (2.3% treatment induced mortality (HD9 trial), 70-80% infertility in men, 51% infertility plus premature menopause in most women over the age of 25, risk of myelodysplasia) can be justified. Furthermore, the increased efficacy of BEACOPP-escalated only translated into a survival benefit for the 20% of patients with the poorest prognosis at diagnosis, suggesting that equivalent results might be achieved with less toxic treatment in the better prognostic groups.

To mitigate the toxicity of BEACOPP-escalated, an alternative approach is to further shorten the cycle duration instead of dose escalation. The GHSG have designed a time-intensified variant of the BEACOPP regimen repeated every 14 days (BEACOPP-14) with G-CSF support [18]. In the multicentre pilot study BEACOPP-14 was shown to be both feasible and effective in a total of 94 patients with advanced Hodgkin lymphoma. 94% of patients achieved a complete remission and the overall survival and FFTF at 34 months were 97% and 90%, respectively. Acute toxicity was moderate, with World Health Organization grade 3/4 leucopenia in 75%, thrombocytopenia in 23%, anaemia in 65%, and infection in 12% of patients. These results showed that dose intensification of BEACOPP-21 by shortening of cycle duration from 3 weeks to 2 weeks with G-CSF support is possible, acute toxicity of BEACOPP-14 is moderate and comparable to that of BEACOPP-21, and treatment results are promising with a low rate of progressive disease (4%) and a FFTF rate of 90% at 34 months. This compares favourably with BEACOPP-escalated (FFTF 90% at 34 months) and is superior to BEACOPP-21 (FFTF 81% at 34 months). This is further supported by the last interim analysis of the HD15 trial which showed there was no significant difference between 6 or 8 cycles of BEACOPP-escalated versus 8 cycles of BEACOPP-14. Therefore in this study,

BEACOPP-14 or BEACOPP-escalated, depending on recruiting centre preference, will be used as the dose escalation regimen in those patients who are PET positive after 2 cycles of ABVD.

Although ABVD remains the standard treatment for advanced Hodgkin lymphoma, there are significant concerns with this regimen regarding the potential for long term cumulative pulmonary toxicity from bleomycin. Many clinicians empirically reduce the bleomycin dose during the latter cycles of treatment, particularly in older patients, but there is no reliable evidence as to whether this is safe to do or whether this conveys a higher risk of lymphoma recurrence. In the recent UK LY09 study, 12% of deaths among those receiving ABVD were caused by respiratory complications, and the administered dose intensity was less than 80% of that planned in 15% of patients[12]. A retrospective series from the Mayo clinic found significant bleomycin-related pulmonary toxicity in 18% of patients, among whom survival was significantly worse, with mortality up to 24% in those with the pulmonary syndrome[19]. Whilst there is a recognition that omitting bleomycin may be desirable for those most at risk, there is no prospective data to confirm that this can be done safely. In the absence of a reliable predictive test for pulmonary fibrosis following bleomycin treatment, it would be useful to know whether the drug could be omitted altogether from treatment once patients are shown to have a high chance of cure following an early PET scan. The GHSG HD13 trial is comparing ABVDx2 vs AVDx2 vs ABVx2 vs AVx2 in patients with stage I-IIA/B Hodgkin lymphoma. Interim analysis after a median observation time of two years, with 200 patients randomized to each arm, has resulted in the closure of arms AV and ABV as there were 4-5 times more HL related events than the other two arms. As the results for the ABVD and AVD arms are similar, the study continues to recruit with more than 300 patients in each arm.

2.4 Rationale for the Study

The aim of this study is to evaluate prospectively the role of FDG-PET imaging after 2 cycles of ABVD chemotherapy in determining response assessment and subsequent management decisions for patients receiving first-line treatment for advanced Hodgkin lymphoma. The results of this study will provide information on the prognostic value of FDG-PET after 2 cycles of therapy and the validity of using these data to influence subsequent treatment. The study aims to identify early in the treatment course those patients unlikely to be cured with standard ABVD treatment, for whom switching to a more intensive regimen may be curative. For those patients who have a good initial response to standard treatment, continuation of ABVD will be compared to the omission of Bleomycin from subsequent cycles, in order to avoid the problem of cumulative pulmonary toxicity.

2.5 Study Objectives

This study will test the hypotheses:

1. Can FDG-PET imaging be reproducibly and effectively applied in the early assessment of response to chemotherapy for a risk-adapted treatment strategy in advanced Hodgkin lymphoma?

2. Can a negative FDG-PET scan after 2 cycles of ABVD chemotherapy be used to predict a group in which it is safe to reduce therapy by the subsequent omission of bleomycin, without detriment to their progression-free survival?

3. Does treatment intensification in response to positive FDG-PET imaging after 2 cycles of ABVD improve the outcome by comparison with previous series?

Primary Outcome Measure: **3 year progression-free survival**

Secondary Outcome Measures: **Overall survival, Toxicity**

2.6 Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA) and other relevant regulatory authorities
- 'Adoption' into NIHR portfolio
- NHS permission
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

3.0: SELECTION OF SITES/SITE INVESTIGATORS

3.1 Site selection

In this protocol trial **"Site"** refers to the hospital or site where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, imaging, follow up schedules and all requirements of the trial protocol
- Requirements of the Research Governance Framework and the Medicines for Human Use (clinical trials) Act (SI 2004/1031 and all amendments)
- Data collection requirements

Non-UK sites must comply with all local regulations governing clinical trials in ABVD and BEACOPP in first line treatment of advanced Hodgkin's lymphoma.

3.1.1 Selection of Principal Investigator and other investigators at sites

Sites must have an appropriate Principal Investigator (PI) i.e. a health care professional authorised by the site, ethics committee and regulatory authority to lead and coordinate the work of the trial on behalf of the site. Other investigators at site wishing to participate in the trial must be trained and approved by the PI; all investigators will be required to sign a

declaration of participation. All investigators must be medical doctors and have experience of treating Hodgkin's Lymphoma.

3.1.2 Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). An up-to-date, signed copy of the CV for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing Institution, or 2 yearly where the Institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

3.2 Site initiation and activation

3.2.1 Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation, with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by teleconference.

3.2.2 Required documentation

The following documentation must be submitted to UCL CTC prior to a site being activated by UCL CTC trial team:

- Trial specific Declaration of Participation/Site Registration Form (identifying relevant local staff)
- All relevant institutional approvals (e.g. local NHS permission)
- A completed site delegation log, signed and dated by the PI
- A copy of the PI's current CV, signed and dated

In addition, the following agreements must be in place:

- For UK sites: a signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually an NHS Trust)
- For non-UK sites: a signed International Clinical Trials Site Agreement (ICTSA).
- For countries with a Country Coordinating Centre (CCC):
    - a signed International Country Coordinating Centre Agreement
    - a signed clinical trial agreement between the CCC and the relevant institution

3.2.3 Site activation letter

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Once the site has been activated by UCL CTC, the PI is responsible for ensuring:

- Adherence to the most recent version of the protocol
- All relevant site staff are trained in the protocol requirements
- Appropriate recruitment and medical care of patients in the trial
- Timely completion and return of CRFs (including assessments of all adverse events)
- Prompt notification and assessment of all serious adverse events
- That the site has facilities to provide **24 hour medical advice** for trial patients

4.0 INFORMED CONSENT

Sites are responsible for assessing a patient's capability to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form. The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions the current approved patient information sheet for the trial should be discussed with the patient. A minimum of twenty four hours must be allowed for the patient to consider and discuss participation in the trial. Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient notes.

Non-UK Sites will need to consent patients to the trial according to local practice and regulatory and/or ethical requirements.

Site staff are responsible for:

- Checking that the correct (current approved) versions of the patient information sheet and consent forms are used
- Checking that information on the consent form is complete and legible
- Checking that the patient has completed/initialled all relevant sections and signed and dated the form
- Checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- Checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- Giving the patient a copy of their signed consent form and patient information sheet
- Following registration: Adding the patient trial number to all copies of the consent form, which should be filed in the medical notes and investigator site file.

Details of the informed consent process will be collected on the patient registration case report form.

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time (see section 14.0 – withdrawal of patients).

5.0 SELECTION OF PATIENTS

5.1 Pre-registration evaluation

The following assessments or procedures are required to evaluate the suitability of patients for the trial:

a) Complete medical history.
b) Concomitant diseases and treatment.
c) Physical examination including height, weight and body surface area.
d) Vital signs.
e) WHO performance status (Appendix 2).
f) Local pathology review.
g) Electrocardiogram, if clinically indicated.
h) Echocardiogram or nuclear medicine scan (MUGA) should be performed if the patient has a past history of cardiac disease or hypertension or an abnormal resting ECG.
i) Contrast enhanced CT scan of the neck, thorax, abdomen and pelvis.
j) FDG-PET-CT scan.
k) Full blood count to include haemoglobin, platelets, ESR/PV, white blood cell count and differential.
l) Serum electrolytes (i.e sodium and potassium), urea and creatinine.
m) Serum bilirubin, liver transaminases i.e. alanine transferase and/or aspartate transferase, alkaline phosphatase, albumin and total proteins.
n) Serum lactate dehydrogenase (LDH).
o) Serum FSH, LH, oestradiol and testosterone levels.
p) Bone marrow trephine biopsy. For patients with stage IIA disease, this can be omitted if the blood count is completely normal.
q) Pulmonary function tests (including spirometry and diffusing capacity).

For anaemic patients please calculate DLCO/TLCO as detailed below:-

EUR Adjusted DLCO (adolescent males and men): Hb adjusted DLCO (DLCOc) = measured DLCO ([10.22 + Hb g/dL]/[1.7 x Hb])

EUR Adjusted DLCO (children <15 y and women): Hb adjusted DLCO (DLCOc) = measured DLCO ([9.38 + Hb g/dL]/[1.7 x Hb])

r) Sperm counts are recommended for men, and cryopreservation should be discussed as appropriate.
s) Negative pregnancy test for women of child bearing potential

Baseline blood tests (full blood count and biochemistry) should be performed within 14 days prior to registration. All other investigations need to be performed within 28 days prior to registration.

If the baseline CT was performed more than 28 days prior to registration, the CT component of the PET-CT must be reviewed to determine whether significant progression has occurred during the interval since the original CT. If progression has occurred the stage will be based upon the later images. Staging will be based upon CT findings only and not the pattern of FDG uptake.

5.2 Screening Log

A screening log must be maintained by the site and kept in the Investigator Site File. This must record all patients identified with Hodgkin's Lymphoma and the reasons why they were not registered in the trial if this is the case. The log must be sent to UCL CTC when requested with patient identifiers removed prior to sending.

5.3 Patient Eligibility

There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed prior to calling/faxing for registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

5.3.1 Patient Inclusion Criteria

1. Histologically confirmed classical Hodgkin lymphoma (HL) according to the current World Health Organisation Classification (nodular sclerosis, mixed cellularity, lymphocyte rich, lymphocyte depleted). All histology will be reviewed by a central pathology panel for the group concerned
2. Aged 18 or above
3. Clinical stage IIB, IIIA, IIIB or IV, or Clinical stage IIA with adverse features:
   - bulk mediastinal disease, defined as maximal transverse diameter of mass >0.33 of the internal thoracic diameter at D5/6 interspace on routine chest X-ray
   - outside the mediastinum, lymph node or lymph node mass greater than 10cm in diameter
   - more than two sites of disease
   - other poor risk features as a result of which it is considered necessary to treat with full course combination chemotherapy
4. No previous chemotherapy, radiotherapy or other investigational drug for HL
5. Performance status 0-3 (Appendix 2)
6. Adequate bone marrow function with platelets > $100x10^9$/l; neutrophils > $1.5x10^9$/l at the time of study entry unless lower numbers are attributed to bone marrow infiltration by lymphoma
7. Serum creatinine less than 150% of the upper limit of normal, serum bilirubin less than twice the upper limit of normal and transaminases < 2.5× upper limit of normal unless attributed to lymphoma
8. Patients with a significant history of ischaemic heart disease or hypertension must have an acceptable left ventricular ejection fraction (LVEF) ≥50%
9. Life expectancy > 3 months

10. All patients of childbearing potential are willing to use adequate contraceptive precautions
11. Written, informed consent
12. Access to an approved PET-CT scanning facility

5.3.2 Exclusion Criteria

1. Poorly controlled Diabetes mellitus
2. Other concurrent uncontrolled medical condition
3. Pregnant or lactating
4. Known central nervous system or meningeal involvement by the lymphoma
5. Cardiac contra-indication to doxorubicin: abnormal contractility on echocardiography or nuclear medicine examination (MUGA)
6. Neurological contra-indication to chemotherapy (e.g. pre-existing neuropathy)
7. General status that does not allow the administration of a full course of chemotherapy according to the investigator
8. Concurrent active malignancy other than fully excised non melanoma skin cancer or squamous cell carcinoma of the cervix. Subjects with previous malignancies are eligible provided they have been disease free for at least 5 years.
9. Known positive serology for HIV, Hepatitis B or Hepatitis C (but no requirement for routine testing in the absence of risk factors)
10. Medical or psychiatric conditions that compromise the patient's ability to give informed consent

5.4 Histological Study

Tissue samples will be sent to the Haematological Malignancy Diagnostic Service (HMDS) in Leeds for Tissue Microarrays studies (TMAs). This will be organised for each case by a panel under the direction of Dr Andrew Jack, Head of Department at the HMDS in Leeds

Following registration, a letter with a pathology registration form will be sent from the UCL CTC to the main trial contact to forward to the local pathologist requesting that a representative histological block be provided for the additional studies.

Sites should send all histological material together with the pathology registration form to:

Dave Blythe
HMDS
Level 3
Bexley Wing
St James's University Hospital
Leeds LS9 7TF

Samples must be identified by a combination of trial number, initials and date of birth, sent in a Jiffy bag or other suitable packaging.

Once samples are processed, HMDS will send the pathology registration form with the block to the UCL CTC and will include the information required for UCL CTC to return the blocks to the sites.

Tissue microarrays will be retained in HMDS until the trial is complete provided that a patient's consent is in place.

5.5 Pregnancy and Birth Control

The effect of exposure on human pregnancy is undetermined for some of the trial drugs, although many have been shown to possess teratogenic effects and embryolethality in pre-clinical studies.

It is unknown whether many of the drugs are excreted in human breast milk. Doxorubicin has been shown to concentrate in human milk, hence patients receiving treatment must not breast feed.

5.5.1 Pregnancy Testing

All women of childbearing potential who are at risk of becoming pregnant must undergo a pregnancy test prior to commencing trial drug administration.

A woman of childbearing potential is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who has not:

- undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- been postmenopausal for 24 consecutive months (i.e. who has had menses at any time in the preceding 24 consecutive months without an alternative medical cause)

5.5.2 Contraceptive Advice

Due to the effects of the trial drugs during pregnancy and lactation, patients must consent to use one of the following acceptable methods of contraception until 1 year post last treatment administration.

Acceptable methods of effective contraception for this trial are:

- Established use of oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository). The use of barrier contraceptives should always be supplemented with the use of a spermicide. The following should be noted:
  - Failure rates indicate that, when used alone, the diaphragm and condom are **not** highly effective forms of contraception. Therefore the use of additional spermicides does confer additional theoretical contraceptive protection.
  - However, spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. Therefore, spermicides are not a barrier method of contraception and must not be used alone.
- Male sterilisation (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate). For female patients, the vasectomised male partners must

be the sole partner for that patient. Please note that sterilisation is not usually regarded as completely reliable enough on its own to ensure that pregnancy can never occur.

- Absolute and continuous abstinence: When this is in line with the preferred and usual lifestyle of the patient. Please note that periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

Male patients with partners of childbearing potential must consent to use acceptable methods of contraception until 1 year post last treatment administration.

Male patients with partners who are pregnant must consent to use condoms until the child is born.

The method(s) of contraception used must be stated in the patient medical notes.

If a patient or the partner of a male trial patient becomes pregnant during the trial UCL CTC must be informed immediately (See section 10.0 (Pharmacovigilance) for details on the reporting procedure).

5.6 Long term infertility

The affect on human fertility is unknown for some of the trial drugs, although some have been shown to cause azoospermia, aspermia and ovarian failure, which may be irreversible.

Infertility in patients might be temporary or permanent. Female patients also might experience an earlier menopause.

It is recommended that men wanting to father children should preserve unexposed sperm prior to commencing chemotherapy.

6.0 REGISTRATION PROCEDURE

6.1 Registration

Patient registration will be undertaken centrally at UCL CTC and this must be performed prior to commencement of any trial treatment.

Following pre-treatment evaluations, (as detailed in section 5.1), confirmation of eligibility and consent of a patient at a site the registration form must be fully completed and then faxed to UCL CTC. The faxed registration form will be used to confirm patient eligibility at UCL CTC.

A trial number will be assigned for the patient and details added to the form.

UCL CTC will fax confirmation of the patient's inclusion in the trial, their trial number to the main contact and pharmacy**.** Case report forms will be sent to the main contact at site.

Registration/Randomisation telephone number:	+44 (0)20 7679 9860
Registration/Randomisation fax number:	+44 (0)20 7679 9861
Office hours:	09:00 to 17:00 Monday to Friday (UK Time)

Once a patient has been registered onto the trial they must be provided with the following:

- A copy of their signed consent form and patient information sheet

7.0 TRIAL TREATMENT

7.1 Treatment summary

For the purpose of this protocol, the IMPs are Doxorubicin, Bleomycin, Vinblastine, Dacarbazine, Cyclophosphamide, Etoposide, Procarbazine, Natulan (to be used if UK licensed procarbazine is unavailable) Prednisolone and Vincristine.

Patients must be registered into the trial before starting treatment. Treatment should start within 14 days after registration. All chemotherapy and supportive medication should be sourced from the hospital pharmacy as per local practice and funded locally and administered in accordance with local practice and the guidelines provided below. Any toxicity grades referred to are from CTCAEv3.0:
(http://ctep.cancer.gov/forms/CTCAEv3.pdf).

To calculate body surface area (BSA) the Dubois formula should be used:

$$BSA(m^2) = 0.007184 \times (\text{patient height in cm})^{0.725} \times (\text{patient weight in kg})^{0.425}$$

7.2 Trial Treatment Details

7.2.1 Initial treatment schedule for all patients

This randomised controlled trial is unblinded for the chemotherapy agents because there is no practical method to achieve blinding.

Patients in need of urgent treatment are permitted to receive steroids up to a dose of 50mg of prednisolone or the equivalent for up to 7 days prior to their trial PET-CT scan.

All patients will receive 2 cycles of ABVD according to the following schedule which should be repeated every 28 days:

Doxorubicin	25 mg/m^2 IV	Days 1 & 15
Bleomycin	10,000 IU/m^2 IV	Days 1 & 15
Vinblastine	6 mg/m^2 IV	Days 1 & 15
Dacarbazine	375 mg/m^2 IV	Days 1 & 15

All drugs will be given at full dose and on schedule, with no dose delays or reductions for haematologic toxicity. **Dose capping is not permitted**, with the exception of very obese patients, where ideal body weight may be used. However, the dose must not be reduced to less than 85% of the dose calculated using actual body weight. Granulocyte colony-stimulating factors are not indicated as a matter of routine[20], but can be used at the discretion of the treating clinician, in accordance with local policy.

A PET-CT scan will then be performed 9 to 13 days after day 15 of the 2nd cycle of ABVD:

PET negative patients will be randomised to continue ABVD or AVD.

PET positive patients will receive BEACOPP-14 or BEACOPP-escalated according to recruiting site preference, determined in advance.

7.2.2 PET negative patients

ABVD (repeated every 28 days for 4 cycles)

Doxorubicin	25 mg/m^2 IV	Days 1 & 15
Bleomycin	10,000 IU/m^2 IV	Days 1 & 15
Vinblastine	6 mg/m^2 IV	Days 1 & 15
Dacarbazine	375 mg/m^2 IV	Days 1 & 15

Guidelines for treatment and dose reductions for ABVD

All drugs will be given at full dose and on schedule, with no dose delays or reductions for haematologic toxicity. **Dose capping is not permitted**, with the exception of very obese patients, where ideal body weight may be used. However, the dose must not be reduced to less than 85% of the dose calculated using actual body weight. Granulocyte colony-stimulating factors are not indicated as a matter of routine[20], but can be used at the discretion of the treating clinician, in accordance with local policy.

Dose modification for hepatic dysfunction:

Serum Bilirubin	**Dose Modification**
1.7-2.5 x upper limit of normal	50% doses of Doxorubicin & Vinblastine 100% dose of Bleomycin & Dacarbazine
2.5-4.0 x upper limit of normal	25% doses of Doxorubicin & Vinblastine 100% dose of Bleomycin & Dacarbazine

Dose modification for neurotoxicity

If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider possible dose reduction of vinblastine. For patients who develop ≥ grade 3 ileus, treatment should be delayed until recovery and vinblastine introduced at 75% of the normal dose thereafter. If ≥ grade 3 ileus recurs, vinblastine should be discontinued.

Dose modification for pulmonary toxicity

All patients complaining of shortness of breath should have a CXR and pulmonary function tests prior to further administration of Bleomycin. Bleomycin should only be discontinued if there are clinical signs or CXR evidence of pulmonary infiltration/fibrosis, or if the transfer factor falls below 50% of the predicted value.

AVD (repeated every 28 days for 4 cycles)

Doxorubicin	25 mg/m^2 IV	Days 1 & 15
Vinblastine	6 mg/m^2 IV	Days 1 & 15
Dacarbazine	375 mg/m^2 IV	Days 1 & 15

Guidelines for treatment and dose reductions for AVD

All drugs will be given at full dose and on schedule, with no dose delays or reductions for haematologic toxicity. **Dose capping is not permitted**, with the exception of very obese patients, where ideal body weight may be used. However, the dose must not be reduced to

less than 85% of the dose calculated using actual body weight. Granulocyte colony-stimulating factors are not indicated as a matter of routine[20], but can be used at the discretion of the treating clinician, in accordance with local policy.

Dose modification for hepatic dysfunction:

Serum Bilirubin	**Dose Modification**
1.7-2.5 x upper limit of normal	50% doses of Doxorubicin & Vinblastine 100% dose of Dacarbazine
2.5-4.0 x upper limit of normal	25% doses of Doxorubicin & Vinblastine 100% dose of Dacarbazine

Dose modification for neurotoxicity

If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider possible dose reduction of vinblastine. For patients who develop ≥ grade 3 ileus, treatment should be delayed until recovery and vinblastine introduced at 75% of the normal dose thereafter. If ≥ grade 3 ileus recurs, vinblastine should be discontinued.

7.2.3 PET positive patients

Prior to receiving either regimen patients may have a peripheral blood progenitor cell harvest performed using cyclophosphamide priming at the treating clinican's discretion. This must be arranged so that the first cycle of BEACOPP-14 or BEACOPP-escalated can be given within 6 weeks of the last dose of ABVD.

BEACOPP-14 (repeated every 14 days for 4 to 6 cycles – see section 1.2)

Doxorubicin	25mg/m^2 iv	Day 1
Cyclophosphamide	650mg/m^2 iv	Day 1
Etoposide	100mg/m^2 iv	Days 1-3
Procarbazine (or Natulan)	100mg/m^2 po	Days 1-7
Prednisolone	80mg/m^2 po	Days 1-7
Bleomycin	10,000units/m^2 iv	Day 8
Vincristine*	1.4mg/m^2iv	Day 8
G-CSF	263/300mcg or equivalent PEG-Filgrastim single dose	Day 9-13

*maximum 2 mg

Guidelines for treatment and dose reductions for BEACOPP-14[18]

Cycles should be repeated on day 15 provided the white cell count > $2.5x10^9$/l and the platelet count > $80x10^9$/l. The day 8 drugs should be given on schedule and at full dose regardless of blood counts.

Dose modification for haematological toxicity:

Delay in white cell count or platelet recovery	Dose Modification
< 1 week	None
1-2 weeks	75% dose of cyclophosphamide, doxorubicin, etoposide, and procarbazine/Natulan
> 2 weeks	50% dose of cyclophosphamide, doxorubicin, etoposide, and procarbazine/Natulan

Dose modification for doxorubicin for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
1.7-2.5 x upper limit of normal	50% dose of doxorubicin
2.5-4.0 x upper limit of normal	25% dose of doxorubicin

Dose modification for etoposide for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
26-51	50% dose of etoposide
>51umol/l	Clinical decision regarding further reduction of etoposide

AST/ALT	Dose Modification
60-180	50% dose of etoposide
>180	Clinical decision regarding further reduction of etoposide

Dose modification for vincristine for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
26-51	50% dose of vincristine*
>51umol/l	50% dose of vincristine if AST/ALT normal, (if AST/ALT>180 consider omission)*

AST/ALT	Dose Modification
60-180	50% dose of vincristine*
>180	Consider omission of vincristine*

*This is recommended although should always be considered whether it is disease related.

Dose modification for procarbazine/Natulan for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
26-51	None
>51umol/l	50% dose of procarbazine/Natulan

Dose modification of cyclophosphamide and bleomycin for renal dysfunction:

Creatinine clearance (mls/min)	Dose Modification
> 50	None
10-50	75% dose of cyclophosphamide and bleomycin
<10	50% dose of cyclophosphamide and bleomycin

Dose modification of etoposide for renal dysfunction:

Creatinine clearance (mls/min)	Dose Modification
< 60	85% dose of etoposide
< 30	75% dose of etoposide

Dose modification of procarbazine/Natulan for renal dysfunction:

Serum creatinine umol/l	Dose Modification
177 or below	None
>177	50% dose of procarbazine/Natulan

Dose modification for neurotoxicity

If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider possible dose reduction of vincristine. For patients who develop ≥ grade 3 ileus, treatment should be delayed until recovery and vincristine introduced at 75% of the normal dose thereafter. If ≥ grade 3 ileus recurs, vincristine should be discontinued.
Dose modification for pulmonary toxicity

All patients complaining of shortness of breath should have a CXR and pulmonary function tests prior to further administration of Bleomycin. Bleomycin should be discontinued if any clinical signs or CXR evidence of pulmonary infiltration/fibrosis develop, or if the transfer factor is <50% of the predicted value.

BEACOPP-escalated (repeated every 21 days for 3 to 4 cycles – see section 1.2)

Doxorubicin	35mg/m^2 iv	Day 1
Cyclophosphamide	1250mg/m^2 iv	Day 1
Etoposide	200mg/m^2 iv	Days 1-3
Procarbazine (or Natulan)	100mg/m^2 po	Days 1-7
Prednisolone	40mg/m^2 po	Days 1-14
Bleomycin	10,000units/m^2 iv	Day 8
Vincristine*	1.4mg/m^2iv	Day 8
G-CSF	263/300mcg or equivalent PEG-Filgrastim single dose	Day 9 until count recovered

*maximum 2 mg

Guidelines for treatment and dose reductions for BEACOPP-escalated

Cycles should be repeated on day 22 provided the white cell count > 2.5x10^9/l and the platelet count > 80x10^9/l. The day 8 drugs should be given on schedule and at full dose regardless of blood counts.

Doses should be reduced in subsequent cycles if predefined toxic effects — CTCAEv3.0 grade 4 leucopenia (<1.0 x 10^9 /L) for more than four days; CTCAE grade 4 thrombocytopenia (<25 x 10^9 /L), infection, or mucositis; or an adverse effect that requires a two-week delay in treatment — occur in a given cycle. After each such event, the doses of cyclophosphamide and etoposide should be reduced by one level on a five-level scale from escalated to standard doses as shown below. If toxic effects occur in two successive cycles, standard doses should be used for all subsequent cycles.

Level 1- escalated dose	Level 2	Level 3	Level 4	Level 5 – standard dose
Cyclophosphamide 1250mg/m^2	1100mg/m^2	950mg/m^2	800 mg/m^2	650 mg/m^2
Etoposide 200 mg/m^2	175mg/m^2	150mg/m^2	125 mg/m^2	100 mg/m^2

Dose modification for doxorubicin for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
1.7-2.5 x upper limit of normal	50% dose of doxorubicin
2.5-4.0 x upper limit of normal	25% dose of doxorubicin

Dose modification for etoposide for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
26-51	50% dose of etoposide
>51umol/l	Clinical decision regarding further reduction of etoposide

AST/ALT	Dose Modification
60-180	50% dose of etoposide
>180	Clinical decision regarding further reduction of etoposide

Dose modification for vincristine for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
26-51	50% dose of vincristine*
>51umol/l	50% dose of vincristine if AST/ALT normal, (if AST/ALT>180 consider omission)*

AST/ALT	Dose Modification
60-180	50% dose of vincristine*
>180	Consider omission of vincristine*

*This is recommended although should always be considered whether it is disease related.

Dose modification for procarbazine/Natulan for hepatic dysfunction:

Serum Bilirubin umol/l	Dose Modification
26-51	None
>51umol/l	50% dose of procarbazine/Natulan

Dose modification of cyclophosphamide and bleomycin for renal dysfunction:

Creatinine clearance (mls/min)	Dose Modification
> 50	None
10-50	75% dose of cyclophosphamide and bleomycin
<10	50% dose of cyclophosphamide and bleomycin

Dose modification of etoposide for renal dysfunction:

Creatinine clearance (mls/min)	Dose Modification
< 60	85% dose of etoposide
< 30	75% dose of etoposide

Dose modification of procarbazine/Natulan for renal dysfunction:

Serum creatinine umol/l	Dose Modification
177 or below	None
>177	50% dose of procarbazine/Natulan

Dose modification for neurotoxicity

If the patient complains of significant constipation or sensory loss in fingers and/or toes, consider possible dose reduction of vincristine. For patients who develop ≥ grade 3 ileus, treatment should be delayed until recovery and vincristine introduced at 75% of the normal dose thereafter. If ≥ grade 3 ileus recurs, vincristine should be discontinued.

Dose modification for pulmonary toxicity

All patients complaining of shortness of breath should have a CXR and pulmonary function tests prior to further administration of Bleomycin. Bleomycin should be discontinued if any clinical signs or CXR evidence of pulmonary infiltration/fibrosis develop, or if the transfer factor is <50% of the predicted value.

7.2.4 Pharmacy responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the Principal Investigator, who may delegate this responsibility to the local pharmacist, or other appropriately qualified personnel, who will be the Pharmacy Lead.

Please see separate trial drug summary document and appendix 3 of the Clinical Trial Site Agreement.

7.2.5 Drug accountability

The Pharmacy Lead will ensure that appropriate records are maintained.

These records must include accountability for each drug including, dispensing, returned medication, and destruction of returned/unused medication. Template accountability forms will be supplied, however, sites may be permitted to use their own drug accountability records providing the same information is captured as a minimum. Such in-house records must be submitted to UCL CTC for review and authorisation for use prior to patient enrolment.

7.2.6 Concomitant medications

These are recommended with all chemotherapy regimens:

1. Allopurinol 300mg od po (100mg if creatinine clearance <20mls/min) for the first four weeks
2. 5-HT_3 antagonist (ondansetron, granisetron, etc.) with each dose of treatment (IV immediately before and orally for 48 hours after) plus metoclopramide or domperidone as required for breakthrough nausea
3. Co-trimoxazole 480mg bd Monday/Wednesday/Friday
4. Mouth care and antacids should be given according to local protocols. A suggested regimen is Nystatin 1ml qds po and Lansoprazole 30mg od po

7.2.7 Other trial interventions

Radiotherapy

It is anticipated that patients who are PET negative after 2 cycles of ABVD will not receive radiotherapy at the end of their treatment.

Patients with a positive interim PET scan after 2 cycles of ABVD, will have a further PET-CT scan 2-6 days after day 8 of the 4th cycle of BEACOPP-14 or 9-13 days after day 8 of the 3rd cycle of BEACOPP-escalated. It will be at the treating physician's discretion whether radiotherapy is given to sites of FDG uptake on completion of chemotherapy to any patient in the PET positive group, although it is anticipated that patients who become PET negative and who are in radiological complete remission will not receive radiotherapy.

The recommended dose for IFRT is 30-36Gy in 1.8-2Gy daily fractions, 5 fractions per week. Patients with a persistently positive PET scan may go on to receive salvage chemotherapy according to local protocols.

8.0 ASSESSMENTS

8.1 Assessment time points

Information is required from patients at the following time points:

- Before each treatment cycle
- After 2 cycles of ABVD
- One month after the end of all treatment
- Follow up

See also the trial investigation schedule (appendix 4).

8.2 Assessments during treatment

During treatment the patient should be seen before each cycle of treatment commences and the following investigations performed:

a) Physical Examination.
b) Toxicity and adverse event assessment.
c) Laboratory tests including full blood count, serum electrolytes, urea, creatinine, bilirubin, liver transaminases, alkaline phosphatase.

8.2.1 After 2 cycles

a) Full body PET-CT scan

This will be performed 9 to 13 days after day 15 of the 2nd cycle of ABVD.

A first scan report will be issued by the PET centre performing the scan using the form shown in Appendix 5. A second report will be issued following central review using the form shown in Appendix 5. For reasons of uniformity it is this second report that will determine subsequent management specified above.

8.2.2 After 4 cycles of BEACOPP-14 or 3 cycles of BEACOPP-escalated

a) Full body PET-CT scan

This will be performed between day 10 and day 14 (2-6 days after day 8 of the 4th cycle) for BEACOPP-14 and between day 17 and 21 (9-13 days after day 8 of the 3rd cycle) for BEACOPP-escalated.

8.3 Assessments on completion of trial treatment

One month after the end of all treatment (i.e. 1 month after completion or chemotherapy or radiotherapy), the patient should be seen and the following investigations performed:

a) Physical examination
b) Toxicity and adverse event assessment
c) Laboratory tests including full blood count, serum electrolytes, urea, creatinine, serum bilirubin, liver transaminases, alkaline phosphatase, lactate dehydrogenase, albumin and total proteins.
d) Pulmonary function tests, including transfer factor.
e) CT scan of chest, abdomen and pelvis (+ neck, if indicated).
f) Bone marrow biopsy if initially involved.
g) Gonadal function tests

Additionally, three months after completing all treatment, the following investigation must be performed:
a) CT scan of chest, abdomen and pelvis (+ neck, if indicated)

8.4 Assessments during follow up

Patients will be followed up for three years in the first instance and tehn annually until death. All patients will be followed up at the following time points after completion of chemotherapy:

- 3-monthly for the first year
- 4-monthly during the second year
- 6-monthly during the third year
- Annually thereafter until death

The following assessments will be carried out during follow up:

a) A physical examination should be done at each follow up visit.
b) CT scan of chest, abdomen and pelvis at 3 months and 12 months after finishing treatment.
c) Full blood count and ESR/PV will be measured at each follow-up visit.
d) Pulmonary function tests, including transfer factor, will be measured annually for 5 years.
e) Toxicity and adverse events assessment
f) Gonadal function will be measured annually

If a patient fails to attend any visit then the site must make every effort to gain follow up information as requested. All efforts should be made by the Site to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site.

Patients will be followed up for three years in the first instance and then until death.

8.5 Central Review of PET-CT scans

Standardisation of the criteria by which PET-CT scans are graded is an important aspect of this study. An International panel has agreed criteria for the grading of the PET-CT scans, as set out in Appendix 5.

Each group participating in the study will arrange central review of the PET-CT images obtained at entry and after 2 cycles of ABVD, to take place before randomisation. Central review of the PET-CT images will also be performed after 4 cycles of BEACOPP-14 or 3 cycles of BEACOPP-escalated. The committee of nominated reviewers will agree the criteria for assigning the results of PET-CT scans in advance, to ensure consistency between the groups. A random sample of scans from different groups will be circulated between the nominated reviewers after 6 months of the trial, in order to determine reproducibility of the gradings.

The results of central review will be notified to the investigator and to the Haematology Trials Group, in order for randomisation to be performed. The result of this will be made available to investigators within 48 hours of the PET-CT being performed, in order to minimise treatment delays.

9.0 RANDOMISATION

Following central review of the images, patient randomisation will be undertaken centrally at UCL CTC.

Sites should fax the Central Review Form with the Randomisation fax cover sheet to UCL CTC.

Registration/Randomisation fax number:	+44 (0)20 7679 9861
Office hours:	09:00 to 17:00 Monday to Friday (UK Time)

PET negative patients will be randomised to either ABVD or AVD. UCL CTC will fax confirmation of randomisation result to the main contact and pharmacy.

PET positive patients will be allocated either BEACOPP-14 or BEACOPP-escalated depending on recruiting site preference, specified at the opening of the study.

10.0 DATA MANAGEMENT GUIDELINES

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data entered onto CRFs must reflect source data at site.

Where supporting documentation (e.g. autopsy reports, pathology reports, CT scan images etc) is being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out to maintain confidentiality in accordance with the Data Protection Act 1988.

10.1 Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

Once completed the original CRFs must be sent to UCL CTC (or via the Country Coordinating Centre (CCC) for non-UK sites) and a copy kept at site. All entries must be clear, legible and written in ball point pen. The use of abbreviations and acronyms must be avoided.

10.2 Corrections to CRFs

Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialled. Correction fluid must not be used. The amended CRF must be sent to UCL CTC or CCC (see above) and a copy retained at site.

10.3 Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site (and CCC if applicable) to ensure there are no blank fields before sending to UCL CTC. When data is unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

10.4 Timelines for data return

UK sites must complete and return CRFs to UCL CTC as soon as possible after patient visit and within a month of the patient being seen.

Non-UK sites with a Country Coordinating Centre must complete and submit CRFs to their CCC within a month of the patient being seen. CCCs must forward all CRFs to UCL CTC within 5 business days of receipt.

Non-UK sites without a Country Coordinating Centre must complete and submit all CRFs to UCL CTC within a month of the patient being assessed.

Sites who persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a 'for cause' monitoring visit. See section 13.3 (Non-Compliance/'for cause' on-site monitoring) for details.

10.5 Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency. Queries on incomplete, inaccurate or inconsistent data will be sent to the data contact at site (or CCC where applicable). When responding to a query, site staff should attach an amended copy of the case report form held at site and send to UCL CTC (or via the CCC if applicable), keeping a copy at site. All amendments must be initialled and dated.

11.0: PHARMACOVIGILANCE

11.1 Definitions of Adverse Events

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6:

Adverse Event (AE)

Any untoward medical occurrence or effect in a patient treated on a trial protocol, which does not necessarily have a causal relationship with a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which **is not consistent** with the applicable trial treatment information.

11.2 Reporting Procedures

11.2.1 All Adverse Events (AEs)

All adverse events that occur between informed consent and 30 days post last trial treatment administration must be recorded in the patient notes and the trial CRFs. Those meeting the definition of a Serious Adverse Event (SAE) must also be reported to the UCL CTC using the trial specific SAE Report. Also refer to section 11.2.2 (Serious Adverse Events (SAEs)).

Pre-existing conditions do not qualify as adverse events unless they worsen.

Overdoses

All accidental or intentional overdoses, whether or not they result in adverse events, must be recorded in the patient notes and CRFs. Overdoses resulting in adverse events are classified as SAEs and must be reported to UCL CTC according to SAE reporting procedures. The fact that an overdose has occurred must be clearly stated on the SAE Report. Also refer to section 11.2.2 (Serious Adverse Events (SAEs)).

Sites must inform UCL CTC immediately when an overdose has been identified. Also refer to section 12.0 (Incident Reporting and Serious Breaches).

Adverse Event Term

An adverse event term needs to be provided for each adverse event, preferably using the term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, available online at: http://ctep.cancer.gov/forms/CTCAEv3.pdf.

Severity

Severity of each adverse event will be determined by using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0 as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/forms/CTCAEv3.pdf. In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria:

1 = Mild (awareness of sign or symptom, but easily tolerated)
2 = Moderate (discomfort enough to cause interference with normal daily activities)
3 = Severe (inability to perform normal daily activities)
4 = Life threatening (immediate risk of death from the reaction as it occurred)
5 = Fatal (the event resulted in death)

Causality

The PI, or other delegated site investigator, must perform an evaluation of causality for each adverse event. Causal relationship to each trial treatment must be determined as follows:

- **None**

There is no evidence of any causal relationship.

- **Unlikely**

There is little evidence to suggest a causal relationship (e.g. because the event did not occur within a reasonable time after administration of a trial treatment). There is another reasonable explanation of the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Possible**

There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of a trial treatment). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).

- **Probable**

There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

- **Definitely**

There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

11.2.2 Serious Adverse Events (SAEs)

All SAEs that occur between informed consent and 30 days post the last trial treatment administration (or after this date if the investigator feels the event is related to the trial medication) must be submitted to UCL CTC by fax within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report Submission

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant section(s) of the trial CRFs:

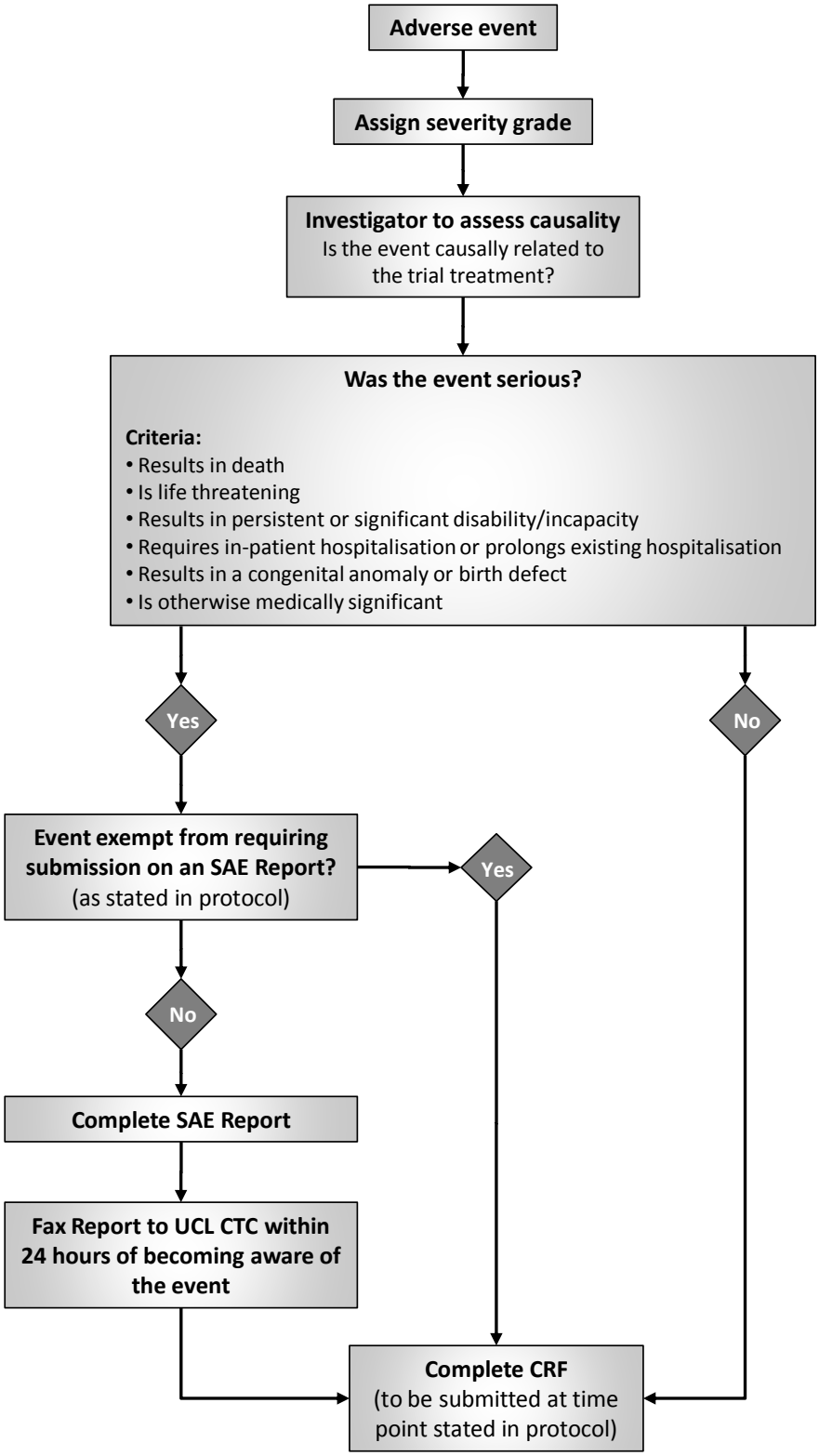
- disease progression (including disease related deaths)
- expected adverse events commonly associated with all of the trial treatment regimens unless they require ITU admission or are fatal:
    - Febrile neutropenia
    - Infection
    - Fever
    - Nausea
    - Vomiting
    - Diarrhoea
    - Haematological toxicity (anaemia, thrombocytopenia, neutropenia)
    - Thrombosis
    - Pain

Please note that hospitalisation for elective treatment or palliative care does not qualify as an SAE.

Completed SAE Reports must be faxed within 24 hours of becoming aware of the event to UCL CTC:

Fax. No: +44 20 7679 9861

Adverse Event Reporting Flowchart



SAE Follow-Up Reports

All SAEs must be followed-up until resolution and until there are no further queries. The PI, or other delegated site investigator, must provide follow-up SAE Reports if the SAE had not resolved at the time the initial report was submitted.

SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the list of expected adverse events in Appendix 3 for the ABVD/AVD and BEACOPP regimens and the current SPCs for Doxorubicin, Bleomycin, Dacarbazine, Vinblastine, Cyclophosphamide, Etoposide, Procarbazine, Prednisolone and Vincristine.

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

11.3 SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the applicable regulatory authority within the EEA and the UK REC within 7 calendar days for fatal/life threatening events, with a follow-up report within a further 8 calendar days, and 15 calendar days for all other events.

Where the SUSAR has occurred outside the UK but within the EEA, UCL CTC will enter the case on the EudraVigilance Clinical Trial Module in order to notify the European Medicines Agency and applicable regulatory authorities. Where the SUSAR has occurred within the UK or outside the EEA, UCL CTC will submit the report directly to the MHRA for them to enter the case on the EudraVigilance Clinical Trial Module.

UCL CTC will also submit the report to country co-ordinating centres/country lead sites (CCCs/CLSs) within 6 calendar days for fatal/life threatening events, with a follow-up report within a further 7 calendar days, and 14 calendar days for all other events**.** CCCs/CLSs must forward all SUSAR reports to their ethics committee(s), as required, and their regulatory authority (for non-EEA countries only), if applicable, within 1 business day. UCL CTC will ensure that consideration is given where the reporting deadline occurs at a weekend to allow reporting within the required timeframes. In the case of conflicting evaluations of causal relationship by the site and UCL CTC/CI, both opinions will be reported.

Informing Sites of SUSARs

UCL CTC will inform all UK PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

For countries outside the UK, UCL CTC will submit reports to CCCs for forwarding to the PIs in their country within one business day. Where there is no CCC, UCL CTC will submit SUSAR reports directly to sites in that country.

11.4 Safety Monitoring

UCL CTC will provide safety information to the TMG and the IDMC on a periodic basis for review.

Trial safety data will be monitored to identify:

- new adverse reactions to the trial treatment regimen or individual trial treatments;
- a higher incidence in rare adverse events than is stated in the SPC for a trial treatment;
- trial related events that are not considered related to the trial treatment regimen.

Should UCL CTC identify or suspect any issues concerning patient safety at any point throughout the trial, the CI or TMG will be consulted for their opinion.

11.5 Pregnancy

If a patient or the partner of a male patient becomes pregnant at any point during the trial treatment and up to one year from the end of trial treatment then a completed trial specific Pregnancy Report must be submitted to UCL CTC by fax within **24 hours** of learning of its occurrence. All pregnancies where last menstrual period (LMP) occurs more than 12 months of stopping trial treatment must be reported on the long term follow up form. If the LMP is unavailable, the estimated date of birth should be more than 21 months after stopping trial treatment. Consent to report information regarding the pregnancy must be obtained from the pregnant patient/partner. The pregnancy monitoring information sheets and consent forms for trial patients and the partners of trial patients must be used for this purpose.

All pregnancies must be reported by faxing a completed Pregnancy Report within 24 hours of becoming aware of the pregnancy to UCL CTC:

Fax. No: +44 (0)20 7679 9861

Pregnancy Follow-Up Reports

All pregnancies must be followed-up until an outcome is determined. For those pregnancies that occurred within 1 year of trial treatment the follow-up Pregnancy Reports must be submitted to UCL CTC by fax within **24 hours** of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment(s) to the pregnancy outcome.

Pregnancies where last menstrual period occurs more than 12 months after stopping trial treatment should be reported on the following long term follow up form.

SAEs during Pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. See section 11.2.2 (Serious Adverse Events (SAEs)) for details.

Pregnancy Report Processing at UCL CTC

UCL CTC will submit a report to the applicable regulatory authority within the EEA, the UK REC and CCCs/CLSs should the pregnancy outcome meet the definition of a SUSAR. Refer to section 11.3 (SUSARs) for details.

11.6 Development Safety Update Reports

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA, the UK REC and all CCCs/CLSs. CCCs/CLSs must forward all reports to the regulatory authority and ethics committee(s) in that country, as required, within 1 business day.

12.0 INCIDENT REPORTING AND SERIOUS BREACHES

Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. UCL CTC may require a report on the incident(s) and a form will be provided if the organisation does not have an appropriate document (e.g. Trust Incident Form for UK sites).

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

Where the incident has occurred in a site outside the UK, the CCC/CLS in that country must also notify the relevant ethics committee in accordance with local requirements. Where UCL CTC identifies an incident at a site outside the UK, the CCC/CLS in the country where the incident occurred will be informed.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

Serious Breaches

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a potential or actual serious breach has been identified, UCL CTC will inform the MHRA within 7 calendar days of becoming aware of the breach.

The serious breach report may also be forwarded to CCCs/CLSs for submission to their regulatory authorities, as required.

UK sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches, 2009).

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

13.0 TRIAL MONITORING AND OVERSIGHT

UK participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form.

Monitoring of non-UK sites will be performed in accordance with the regulatory requirements of each country.

13.1 Central monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial monitoring plan or on request and these will be checked for consistency and completeness. Also refer to sections 3.2.2 (Required Documentation) and 5.2 (Screening Logs).

Eligibility of all patients entered in the trial is assessed by the PI, or, if delegated by the PI, other appropriately trained site staff. Checks of the criteria listed on the registration form will be undertaken by an appropriately trained UCL CTC staff member prior to registration. Also refer to section 6.1 (Registration).

Copies of completed drug accountability logs will be collected at UCL CTC for all trial patients. Sites will be required to submit logs at the frequency detailed in the trial monitoring plan or on request. A proportion of these will be monitored centrally to ensure completeness and correlation with data captured in the CRF. Also refer to section 7.2.5 (Drug Accountability).

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy File at the frequency detailed in the trial monitoring plan. Checklists detailing the current version/date of version controlled documents will be provided for this purpose.

Data received at UCL CTC will be subject to review in accordance with section 10.5 (Data Queries).

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered, indication that dose modification rules for an IMP were not observed following an adverse reaction, etc.), the matter will be raised urgently with site staff and escalated as appropriate (refer to section 12 (Incident Reporting and Serious Breaches) and 13.2 ('For cause' on-site monitoring) for further details).

13.2 'For cause' on-site monitoring

On-site monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements. Sites

will be sent a letter in advance outlining the reason(s) for the visit. The letter will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities, who will be performing the visit and when the visit is likely to occur.

Following a monitoring visit, the Trial Monitor/Trial Coordinator will provide a report to the site, which will summarise the documents reviewed and a statement of findings, deviations, deficiencies, conclusions, actions taken and actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed (this may be delegated to an appropriate member of staff).

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 12.0 (Incident Reporting and Serious Breaches) for details.

13.3 Oversight Committees

13.3.1 Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and RATHL trial staff from UCL CTC (see page 2). The TMG will be responsible for overseeing the trial. The group will meet regularly twice a year and will send updates to PIs (via newsletters) and to the NCRI Lymphoma Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and/or MHRA, Läkemedelsverket (Swedish Medicine Products Agency), Statens Legemiddelverk (Norwegian Medicines Agency) and Irish Medicines Board. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

A charter, signed by the members of the TMG, is in place for this trial.

13.3.2 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and Sponsor.

A charter, signed by the members of the TSC, is in place for this trial.

13.3.3 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held annually to review and address any issues. The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

A charter, signed by the members of the IDMC, is in place for this trial.

13.3.4 Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 11.0 (Pharmacovigilance).

14.0 WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, follow-up and data collection.

Withdrawal from Trial Treatment

A patient may be withdrawn from trial treatment whenever continued participation is no longer in the patient's best interests, but the reasons for doing so must be recorded. Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- Intercurrent illness which prevents further treatment
- Patients withdrawing consent to further trial treatment
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion

In these cases patients remain within the trial for the purposes of follow-up and data analysis according to the treatment option to which they have been allocated. If a patient wishes to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used.

Withdrawal of Consent to Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected and recorded on the relevant CRF and UCL CTC notified in writing. In this event details should be recorded in the patient's hospital records, no further CRFs must be completed and no further data sent to UCL CTC (or CCC for non-UK sites).

Losses to follow-up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team who must be informed of the transfer of care and follow up arrangements.

If a patient is lost to follow-up at a site every effort should be made to contact the patient's GP (if consented) to obtain information on the patient's status.

15.0 TRIAL CLOSURE

15.1 End of Trial

For regulatory purposes the end of the trial will be 5 years after recruitment has been completed and survival data have been published at which point the 'declaration of end of trial' form will be submitted to participating regulatory authorities and ethical committees, as required. However, this will be followed by the non-interventional phase of long-term follow-up, which will continue indefinitely.

15.2 Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of Principal Investigators to ensure data and all essential documents relating to the trial held at site are retained for a minimum of 5 years after the end of the trial, in accordance with national legislation and for the maximum period of time permitted by the site.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of Good Clinical Practice and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

15.3 Early discontinuation of trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 13.4.2 TSC and 13.4.3 IDMC). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

15.4 Withdrawal from trial participation by a site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for all patients recruited into the trial at that site and other responsibilities continue as per CTSA.

16.0: OUTCOME MEASURES AND STATISTICS

16.1 Primary outcomes

3 year progression-free survival

This will be measured from date of registration to date of first appearance of disease progression, relapse or death from any cause. Patients alive without progression or relapse will be censored at date last known to be alive.

Overall survival

This will be measured from date of registration to date of death from any cause; surviving patients will be censored at date last known to be alive.

Toxicity

Acute and chronic using NCI criteria (http://ctep.cancer.gov/forms/CTCAEv3.pdf).

16.2 Statistical considerations

For the patients who become PET-negative, the study is designed to investigate whether equivalent results can be obtained following omission of bleomycin from subsequent cycles. The following assumptions underlie the power calculations:

1. 75% of patients become PET negative after 2 cycles. In the two largest series reported to date the figures are 74% [7] and 81% respectively [9].

2. In the group becoming PET negative at 2 cycles, the 3 year progression-free survival is 95%. Again this is based upon the published figures.

3. A progression-free survival difference of under 5% would need to be excluded to confirm equivalence.

4. A one-sided power calculation is appropriate for de-escalation of therapy where disease control will be the principal endpoint.

With 1200 patients entered in 3 years and a further 3 years follow-up, the study will reliably exclude the chance that AVD is more than 5% worse in 3-year PFS than ABVD:

- Sample size table for a **non-inferiority design** with 90% power and 2.5% (one-sided) (3 years accrual plus 3 years follow-up):

3 year PFS in PET-		Difference		Total number of		
ABVD	AVD	3-year PFS	HR	Events	PET- pts	All pts
95%	90.4%	4.6%	1.97	101	936	1248

As a guideline, if there was good evidence (over 90% power, at least a total of 39 events in PFS) that the PFS in AVD arm was 10% (or hazard ratio (AVD/ABVD) =3.168) worse than that in the ABVD arm this would be a trigger to suspend randomisation.

No randomised comparison is proposed for the group remaining PET-positive after 2 cycles of ABVD. The outcomes for such patients in the series already reported demonstrate such a poor outcome (virtually 100% treatment failure by 2 years) that continuation of standard ABVD would be impossible to justify.

All such patients will therefore receive BEACOPP-14 or BEACOPP-escalated, aiming for a 2-year PFS of 50%. With a total of 300 patients the PFS would be reliably estimated with a standard error of <3%. We will use stopping rules for the PET+ group to address both excessive toxicity or lack of efficacy, in order to restrict the sample size.

The safety and efficacy of the study will be reviewed by the Independent Data Monitoring Committee (IDMC) regularly. In particular, the IDMC will be asked to review the safety and efficacy data of BEACOPP-14 and BEACOPP-escalated regimens. As a guideline, if there was evidence that the 2year-PFS rates were less than 30%, the treatment of BEACOPP-14 or BEACOPP-escalated would be reconsidered. More specifically, using the Simon two-stage optimal design (with 2-year PFS rate 30% vs 50%, significance level 5%, one sided, and power 90%), the efficacy data will be reviewed when 24 and 63 patients have received BEACOPP-14 or BEACOPP-escalated regimens respectively. If more than 16 of the first 24, or 39 of the first 63, patients showed progression within 2-years, the BEACOPP regimens would be reconsidered.

16.3 Secondary objectives

Correlative studies will be carried out under the direction of the various collaborating groups. These will include:

- Prospective plasma and serum collection for novel prognostic markers
- Isolation of genomic DNA for studies of genotype in relation to response.
- Studies of gonadal function

17.0 : ETHICAL AND REGULATORY APPROVALS

In conducting the Trial the Sponsor, UCL CTC and sites shall also comply with all laws and statutes, as amended from time to time, applicable to the performance of clinical trials including, but not limited to:

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) and any applicable local GCP laws or regulations in the relevant countries
- the Human Rights Act 1998
- the Data Protection Act 1998
- the Freedom of Information Act 2000
- the Human Tissue Act 2004

- the Medicines Act 1968
- the Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the Research Governance Framework for Health and Social Care, issued by the UK Department of Health (Second Edition 2005) or the Scottish Health Department Research Governance Framework for Health and Community Care (Second Edition 2006)

All non-UK sites shall comply with all their local laws and statutes applicable to the performance of clinical trials.

17.1 Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled "Ethical Principles for Medical Research Involving Human Subjects" (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the South Central – Southampton B Research Ethics Committee (formerly Southampton & South West Hampshire REC B).

UCL CTC will submit Annual Progress Reports to the REC, which will commence one year from the date of ethical approval for the trial.

17.2 Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA, Läkemedelsverket (Swedish Medicine Products Agency), Statens Legemiddelverk (Norwegian Medicines Agency) and Irish Medicines Board.

17.3 Site Approvals

Evidence of local Trust R&D approval must be provided to UCL CTC prior to site activation. The trial will only be conducted at sites where all necessary approvals for the trial have been obtained.

All non-UK sites must provide confirmation of approval of their local institution(s).

17.4 Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approvals, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for gaining local Trust R&D acknowledgement for all amendments and approval for substantial amendments, and for providing UCL CTC with evidence of this.

17.5 Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number will be required for the registration process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 1998 with the Data Protection Officer at UCL.

18.0 SPONSORSHIP AND INDEMNITY

18.1 Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Sponsor Contact:	Managing Director Research Support Centre
Tel:	+44 (0)20 3447 9995/2178 (unit admin)
Fax:	+44 (0)20 3447 9937

18.2 Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach of the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to claim for compensation should do so by writing in the first instance to the Chief Investigator, who will pass the claim on to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London on request.

19.0 FUNDING

Cancer Research UK is supporting the central coordination of the trial through UCL CTC.

20.0 PUBLICATION POLICY

All publications and presentations relating to the trial will be authorised by the TMG. The first publication of the trial results will be in the name of the TMG, if this does not conflict with the journal's policy. The TMG will form the basis of the writing committee and advise on the nature of publications. Publication will follow the rules of the NCRI lymphoma CSG. Authorship will include the Chief Investigator, trial statistician, a representative of the HTG, a member of the histopathology review team, a member of the PET review team and one additional author from each centre entering more than 5% of the patients. Contributing site investigators in this trial will also be acknowledged. Data from all sites will be analysed together and published as soon as possible. Participating sites may not publish trial results prior to the first publication by the TMG or without prior written consent from the TMG.

The trial data is owned by UCL CTC. The EudraCT number (2007-006064-30) or the clinicaltrials.gov number (NCT00678327) will be quoted in any publications resulting from this trial.

21.0 REFERENCES

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Appendix 1: ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
BD	'Bis Die' – twice daily
BL	Burkitt's Lymphoma
R-CHOP chemotherapy	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone
CCC	Country Co-ordinating Centre
CI	Chief Investigator
CLS	Country Lead Site
CNS	Central Nervous System
CR	Complete response
Cru	Complete Response undocumented/unconfirmed
CRF	Case Report Form
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTAAC	Clinical Trials Advisory & Awards Committee
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
CXR	Chest X-Ray
DFS	Disease Free Survival
DPA	Data Protection Act
DLBCL	Diffuse large B-Cell
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetra Acetate
EEA	European Economic Area
ESR	Erythrocyte Sedimentation Rate
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
G-CSF	Granulocyte Colony Stimulating Factor
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GFR	Glomerular Filtration Rate
GP	General Practitioner
HDT	High Dose Therapy
HGNHL	High Grade Non-Hodgkin's Lymphoma
HMDS	Haematological Malignancy Diagnostic Service
IB	Investigator Brochure

ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IPI	International Prognostic index
ISRCTN	International Standard Randomised Controlled Trial Number
IT	Intrathecal
IUD	Intrauterine Device
IV	Intravenous
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LRF	Leukaemia Research Fund
LVEF	Left Ventricular Ejection Fraction
MRC	Medical Research Council
MRI	Magnetic Resonance Imaging
MHRA	Medicines and Healthcare products Regulatory Agency
MUGA	Multi Gated Acquisition
NCRI	National Cancer Research Institute
NCRN	National Cancer Research Network
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service
NICE	National Institute of Clinical Excellence
NRES	National Research Ethics Service
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PO	By mouth
PR	Partial Response
PV	Plasma Viscosity
R&D	Research & Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group

TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
ULN	Upper Limit of Normal
WBC	White Blood Cells
WCBP	Woman of Child Bearing potential

Appendix 2: WHO PERFORMANCE STATUS

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

Appendix 3: EXPECTED ADVERSE EVENTS

AEs expected for Treatment regimens

Certain AEs are expected for the ABVD/AVD and BEACOPP regimens as a whole (see references 22-28). The following AEs are commonly associated with all trial treatment regimens and will be considered expected for each of the trial drugs. Events marked with an asterisk (*) should be regarded as expected even if fatal.

Fatigue	GI tract toxicity (cont):
Fever	- Constipation
Febrile neutropenia	- Dysphagia
Infection * (all sites and pathogens)	Cardiac toxicity *
Allergy	Phlebitis
Haematological toxicity:	Thromboembolic events *
- Anaemia	Alopecia
- Leucopenia (including neutropenia)	Skin rash
- Thrombocytopenia	Respiratory tract/pulmonary toxicity: *
- Myelosuppression	- Dyspnoea
Neuropathy	- Fibrosis
Neurotoxicity	- Pneumonitis
GI tract toxicity:	- Acute respiratory distress syndrome
- Nausea	Pain
- Vomiting	Secondary malignancy (acute leukaemia, myelodysplastic syndrome, non-Hodgkin's lymphoma, solid tumours)
- Mucositis	
- Diarrhoea	

AEs expected for individual IMPs

Where the event does not appear in the above list of expected AEs for the treatment regimens, the most recent SPC for each of the IMPs will be checked.

Appendix 4: FOLLOW UP SCHEDULE & INVESTIGATIONS

	Pre-treatment screening/staging (-4 to 0 weeks)	Prior to each cycle of chemotherapy	After 2 cycles of ABVD chemotherapy	If PET +ve on 1st response scan, 2nd response scan	After the end of all treatment	3 months after the end of all treatment	6 months after the end of all treatment	9 months after the end of all treatment	12 months after the end of all treatment	Follow-up
Clinical assessments										
Informed consent	×									
History	×	×			×	×	×	×	×	×
Physical examination	×	×			×	×	×	×	×	×
WHO Performance status	×				×	×	×	×	×	×
Adverse events	×	×			×	×	×	×	×	×
Pulmonary tests	×				x				x	x
Gonadal functions	x				x					x
Cardiac assessment										
Electro-cardiogram[a]	×									
Echocardiogram[a]	×									
Imaging										
CT-PET	×		×	x						
CT	x				x	x			x	
Laboratory assessments										
Serum biochemistry[b]	×	×			×					
Haematology[c]	×	×			×	×	×	×	×	×
Pregnancy test[d]	x									
Bone marrow biopsy	×				×[e]					
Pathology review[f]	×									

[a] If clinically indicated
[b] Serum chemistry to include U+E (i.e. urea, sodium and potassium), creatinine, LFT's (i.e. alanine transferase and/or aspartate transferase, alkaline phosphatase, lactate dehydrogenase, albumin and total proteins).
[c] Full blood count to include haemoglobin, platelets, ESR/PV, white blood cell count and differential. ESR/PV does not need to be done prior to each cycle of chemotherapy.
[d] In women of childbearing potential
[e] If involved at presentation.
[f] Diagnostic histological material to be forwarded to HMDS for the making and storage of tissue micro arrays

Appendix 5: PET PROTOCOLS AND PROCEDURES

Introduction

PET has been used in the clinical practice of oncology for over 15 years. However this is the first multinational study to be set up internationally which will use PET-CT for treatment adapted response. The study represents an exciting opportunity for international collaboration for the benefit of patients.

The study will involve patients with advanced Hodgkin Lymphoma (HL) undergoing PET-CT scans at diagnosis and then at key points in their management to make decisions about treatment, including the duration and regime of chemotherapy and the requirement for radiotherapy. Published evidence suggests that PET-CT is the best prognostic indicator available for HD. PET-CT will be used to escalate treatment in patients with poor prognosis and to reduce treatment in patients with good prognosis.

To ensure the highest standards and consistency between PET-CT scanning facilities in different countries, centres of excellence with experience in PET (and more recently PET-CT) will be identified in Europe and the US to act as 'core labs'. The role of the core labs will be to co-ordinate the studies for their region, ensure adequate quality control is carried out at all participating centres and to act as a central reporting facility. Collaboration between core labs to ensure consistency of reporting will enable standards to be set which can be applied across the international community. Links between core labs and other PET scanning facilities will enable sharing of knowledge and hopefully ensure that results from this trial will be applicable in years to come. Central servers will be enable images to be shared across continents and within regions with 'real-time' reporting and debate.

In Europe, potential sites for core labs have been identified in Denmark, Italy, Sweden and the UK. Potential sites for core labs in North America will also be identified by the groups taking part in the study.

Contributors:

Dr S Barrington & Dr M O'Doherty, Guy's & St Thomas's, London
Dr A Gallamini & Dr A. Biggi, Azienda Ospedaliera S. Croce e Carle, Cuneo, Italy
Dr A Quon, Stanford University, USA
Dr M Juweid, University of Iowa, USA
Dr E Brun, University of Lund, Sweden
Dr R Elstrom, University of Michigan, Ann Arbor, USA

PET - CT SCANNING

PET/CT scans with ^{18}Fluorine- fluorodeoxyglucose (FDG) will be performed at baseline and after 2 cycles of chemotherapy ABVD. Patients who are 'negative' after 2 cycles have no further PET/CT scans. Patients with 'positive scans' will have a third PET/CT scan after 4 cycles of BEACOPP-14.

PET scans:

All patients should have a pre-treatment FDG-PET/CT scan as a baseline to be compared with subsequent scans to assess response. This should be performed within 28 days prior to registration'. The CT component of the staging scan may be performed with intravenous and/or bowel contrast if this will replace the staging diagnostic CT scan but the response scan MUST be performed WITHOUT bowel contrast other than water (and WITHOUT intravenous contrast). Response scans must be performed at the same centre and on the same scanner as the baseline scan.

Response scans will be performed at the designated part of the treatment plan between 9-13 days after the preceding dose of chemotherapy. The second PET scan will be booked at the time of starting treatment, to ensure appropriate timing of response scans. In case of treatment delay, PET will need to be rescheduled to fit into the 9-13 day time window. When a third scan is required in patients who are PET positive after 2 cycles the PET-CT scan should be performed:
2-6 days after day 8 of cycle 4 in patients receiving BEACOPP-14
or 9-13 days after day 8 of cycle 3 in patients receiving Escalated BEACOPP.

Scanning Facilities

- Only full-ring dedicated PET-CT scanners are acceptable.
- A documented daily quality control procedure must be in place and records kept.
- A tested and secure method must be used to transfer anonymised scan data between scanning facilities and the core lab (central reporting facility) and an agreed file naming convention adhered to.
- Named persons (and their deputies) should be identified with responsibility for scanning, QC and data transfer at participating PET-CT centres.
- It must be demonstrated that image quality is comparable between centres and standard uptake values can be reliably determined from the PET/CT images.

Detailed information relating to the above is given in the QC document (included later in the appendix).

Scanning cannot start until written confirmation of compliance with the study requirements specified in the QC document is received from the core lab.

Scanning Protocol

Patient preparation

Non-diabetic patients should fast for at least 4 hours prior to the scan. Plain (unflavoured water) should be taken during the period of fasting and the uptake period to ensure good hydration.

Diabetic patients on oral medication should ideally be given a morning appointment and asked to fast for at least 4 hours and omit their hypoglycaemic medication that morning. If it is not possible for a morning appointment to be arranged, a light breakfast can be taken with morning medication. Patients on insulin should eat and administer insulin as usual.

Blood glucose of all patients should be measured on arrival and consideration given to rescheduling the scan if BM measures > 11mM/l (>200mg/dl). **Insulin should not be administered to reduce glucose level.**

Oral diazepam (5-10mg po)-may be given if desired to reduce brown fat uptake 30-60 minutes prior to tracer injection.

Detailed scanning protocol

1. Administer 350 - 550 MBq ^{18}F- FDG for 2D acquisition or 150-350 MBq for 3D acquisition dependant on local imaging criteria and country specific diagnostic reference levels..
2. Emission part of the scan should start at 60 or maximum 70 minutes after injection. If the scan acquisition is not started between 55-80 minutes after injection the patient will be excluded from the study.
3. The response scans must be performed at the same time after injection as the baseline scan $\pm$ 15 minutes, but no earlier than 55 minutes after injection. PET-CT Response scans must be done WITHOUT bowel contrast (other than water) and WITHOUT intravenous contrast
4. Perform attenuation corrected 'half-body' PET-CT scan to cover the area from the base of the brain to mid-thigh using the CT of the PET - CT scanner.
5. Perform head and neck scan if required to cover sites of disease.

6. Patients should be scanned with arms above the head for the body scan (if tolerated) and by the side for head and neck scan if acquired.

Acquisition should be performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc. Images should be reconstructed using OSEM or a similar reconstruction algorithm. Both attenuation-corrected and non attenuation-corrected images should be reconstructed. The proposed data acquisition/reconstruction protocol (including details of all the parameters above) must be agreed with the core lab prior to the start of the study.

Information to be recorded for each patient

For each patient study data acquisition information and patient information must be recorded on the PET-CT acquisition form (included later in the appendix) and forwarded to the core lab.

Image data transfer

Image data must be transferred to the core lab at the same time as the completed PET-CT acquisition form (included later in the appendix).

The following files are required

- Attenuation corrected half body images (cerebellum to mid thigh)
- Non-attenuation corrected half body images
- Half body CT scan
- Attenuation corrected view of head and neck (if performed)
- Non-attenuation corrected view of head and neck (if performed)
- Head and neck CT scan (if performed)

All image files must be compliant with DICOM PART 10 format. It is highly recommended that CD's or images be created and sent directly from the acquisition PET/CT workstation rather than from a secondary PACS system or file library. Specifically, image files that have been converted to savescreens and then reconverted back to DICOM format are NOT acceptable.

Projection images (MIPs) are not required

All files must be clearly named using a pre-arranged filename convention. Central servers at core labs with links to peripheral PET scanning facilities will enable data to be transferred securely and reliably within regions and across continents.

Reporting

PET-CT scans will be reviewed and scored by two named doctors at the core lab, who are blinded to the patient's clinical status. Visual interpretation will be used. Differences in reporting will be resolved by consensus between two doctors at the

same core lab or by a third doctor at another core lab where agreement cannot be reached.

A local report may also be issued but it is the score from the core lab that will be used to determine subsequent treatment for trial purposes.

The PET-CT response scans will be scored with reference to sites of presumed lymphomatous involvement on the PET-CT staging scan

Negative

1	no uptake
2	uptake ≤ mediastinum
3	uptake > mediastinum but ≤ liver

NOTE if mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver=score 2; lesion uptake equal to liver=score 3)

Positive

4	moderately increased uptake compared to liver at any site
5	markedly increased uptake compared to liver at any site
X	new areas of uptake unlikely to be related to lymphoma

Scores 1, 2, 3 with uptake in sites abnormal on the staging scan equal or less than liver uptake will be regarded as 'negative' for disease and scores 4, 5 with uptake greater than liver will be regarded as 'positive' for disease. A separate analysis will be performed on patients with a score of 3 whose scan findings are analogous to the concept of 'minimal residual disease' (MRU) referred to in earlier published data on the use of PET in lymphoma. However for the purposes of treatment, patients with a score of 3 will be regarded as negative for disease. Scores 1X, 2X or 3X will also be regarded as 'negative' for lymphoma.

Standard uptake values (SUVs) will be used to quantify tracer uptake, and response to therapy will be determined by the change in SUV for scans acquired before and after therapy. The change in SUV will be correlated with actual prognosis to test the possibility of defining "quantitative response categories" which may have prognostic value. SUV values will be used in a post hoc analysis and the most appropriate measure to be used will be determined. The use of SUV max and variations of SUV max will be used in this analysis.

Agreement between core labs

Prior to the beginning of the study a "reference set" of ten scans, labeled 1-10 will be sent to the core labs. This will be followed by a 'training set' of 50 patient scans which will be read by the designated reporters at each core lab to facilitate development of a consensus for scan interpretation. The level of agreement between core labs will be measured for this training set. In addition, the first ten scans reported by each core lab will be reviewed by all labs and 10% of the scans annually thereafter.

Radiation Dosimetry

The effective dose associated with an administration of 400 MBq 18-FDG is 8.0 mSv (ARSAC Notes for Guidance 2006). The target organ is the bladder wall, which will receive 68.0 mGy (ICRP Publication 53). The CT attenuation correction using 80 mA and 140 kV will be approximately 8 mSv for the half body. (This will be country specific).

National regulations must be complied with in regard to the administration of radioactive substances and the CT exposure for the purpose of this study.

PET/CT QC procedures

Careful quality control is essential for the success of multi-centre trials such as this one. There are currently no standards for performing multi-centre trials with PET and PET/CT, though such standards are being developed by the professional organisations. The procedures below are based on those of the American College of Radiology Imaging Network.

The study can not start and no patients are to be scanned until all of the following have been completed :

1. The PET/CT scan quality control document (see below) must be completed and forwarded to the core lab.
2. Initial 'start-up' scanner quality control procedures must be performed
3. Two representative patient studies must be transferred to the core lab.
4. The data transfer and anonymization procedure must be set up and validated
5. Written confirmation from the core lab that scanning can now start at your centre must be received.

Initial start-up QC procedures

The restriction of the study to full ring dedicated PET-CT cameras should ensure that the images acquired at all centres are of a comparable quality. In order to confirm this and check the SUV accuracy of each scanner, a phantom should be scanned at each of the participating centres using the local study protocol. This could be done by a representative from the core lab who visits the scanning facility or a representative at the scanning facility if approved by the core lab. Ideally however a personal visit from the core lab to scanning facilities is useful to establish contact and answer individual questions relating to the study for smooth running of the study. The phantom will consist of the EU chest phantom, filled with water throughout, containing 6 small spheres. The test may also be performed using the 'body phantom' and 'six fillable spheres' described in the image quality test from the NEMA Standards Publication NU 2-2001. The spheres will be filled with 25 kBq/ml of ^{18}F- solution and the rest of the phantom with 5 kBq/ml of ^{18}F- to simulate small regions of tracer uptake in the abdomen. Data will be acquired using the same acquisition and processing parameters that will be used for the patient studies. These parameters may vary between sites. Data will be evaluated in terms of absolute activity measurements for the background and the spheres. Two nuclear medicine physicians or radiologists trained in PET/CT will also assess the visual quality of the scans. If significant disparities are observed, for example, from the use of widely differing reconstruction parameters, these will be resolved prior to the start of the study.

The phantom images will be assessed at the core lab.

As this study uses SUVs defined in terms of patient weight, the scales used to weigh the patients must be accurate to within 10% of a standard weight of 70 kg.
This must be demonstrated as part of the initial QC.

Representative patient studies

Two anonymised patient studies (attenuation corrected PET, CT and non-attenuation corrected PET) acquired using the proposed study protocol should be transferred to the core lab.

Data Format and Archiving

All studies to be transferred to the core lab (attenuation corrected PET, non attenuation corrected PET, and CT) must be in DICOM format. BMP files, jpeg files, screen saves and hard copies are not acceptable. Further, many PACS systems convert DICOM images to another format and then reconvert them back to DICOM when exporting to a CD or FTP. This is not acceptable. Raw data must be archived according to local protocol, and at least until the images have been accepted by the core lab.

Data transfer and anonymisation procedure

All patient identifying information must be removed from the images prior to transfer. A procedure for naming, anonymising and transferring studies from the scanning site must be established. This will vary between sites. This can be validated when transferring the test phantom and patient data as above.

Routine scanner QC procedures

A documented scanner quality assurance program must be in place and records kept, covering daily, monthly, quarterly and annual QC testing. The QC procedures must also be sent to the core lab along with example results. The routine CT QC must include a water filled phantom scanned on a weekly basis, to measure image noise and CT number as described in IPEM (Institute of Physics and Engineering in Medicine) report 91.

Additional scanner QC required during the trial

A uniform phantom must be scanned prior to the start of each scanning session in which a patient is to be scanned as part of the trial. This can either be a resin Ge68 phantom (where available) or an F18 water filled phantom. The activity concentration in the F18 phantom should be approximately 5kBq/ml. The average SUV for a large ROI placed at the centre of the phantom must be 1 $\pm$ 10% and on visual inspection the image should show no artefacts. The relevant sections of the patient data sheet must be completed to confirm the results of this test. The F18 or Ge68 phantom images must be sent, with the patient images to the core lab. If the test fails the named physicist at the core lab

should be contacted. The scan must not take place until the reason for this failure has been resolved.

The weighing machine must be checked using a standard weight at least annually and records kept.

Confirmation that study can start at your site

When all the above has been completed a letter will be forwarded to both the PET centre and the Trials Unit to confirm that the centre can now participate in the trial. No subjects should be scanned before this.

Contact

For enquiries relating to the scanning protocol, quality control and data transfer only please contact the Trials Physicist at the core lab:

phone number, email address

For all other enquiries please contact the Trials Unit

PET/CT SCAN QUALITY CONTROL DOCUMENT

Please complete this document and return to the Trials Physicist, address, person@email_address before any patient from the trial undergoes a PET/CT scan.

Contacts at scanning site

Person responsible for performing the scanning procedures (and a deputy to cover leave)

Name
Telephone
Email

Person responsible for ensuring adherence to quality control procedures (and a deputy to cover leave)

Name
Telephone
Email

Person responsible for anonymisation and data transfer (and a deputy to cover leave)

Name
Telephone
Email

Scanner technical specification

Please confirm that you have a:

Full ring PET-CT camera	YES	NO

Please state:	
Manufacturer and Model:	
Date of installation:	
Axial field of view:	
Sensitivity in cps/MBq/ml for uniform 20cm cylinder:	

Quality Control Procedures

Is a documented quality QA program in place	YES	NO

Setup and Normalisation

The frequency at which the PM tubes of the PET scanner are set-up is:	
The frequency at which normalisation is carried out on the PET scanner is:	

Daily and Weekly PET and CT Checks

CT tube warm up and air calibration are carried out on a daily basis	YES	NO
Manufacturer's recommended daily PET QC test carried out YES/NO (measured in cps/kBq/ml for a uniform 20cm phantom)	YES	NO
CT number and noise are measured on a weekly basis (described in IPEM report 91)	YES	NO

Monthly/Annual Quality Control

Sensitivity of the PET scanner checked on at least an annual basis	YES	NO
Annual CT checks are carried out by CT experts on an annual basis (described in IPEM report 91)	YES	NO
PET/CT scanner alignment is checked on at least an annual basis	YES	NO

Additional Procedures to be Undertaken as Part Of This Study

Scan of a uniform F18/Ge68 phantom will be carried out to checkimage quality and confirm that SUV measures 1 $\pm$ 10%, on the morning of the study	YES	NO
QC of the weighing scales will be carried out at least annually	YES	NO
If any of the procedures described in this document cannot be carried out for whatever reason a physicist from the core lab will be contacted immediately and no further studies will be undertaken by your centre until the issues have been resolved	YES	NO

Data Acquisition and Reconstruction

Please supply the following information for the protocol to be used in this study, this will be the protocol used for all data acquired at your centre as part of this trial:

Half body emission scan duration per bed position (give time in minutes)	
Acquisition mode (specify 2D or 3D)	

CT details for half body attenuation correction:

MAs:		kV_p:		pitch:		slice thickness (mm)	

Emission scan reconstruction parameters:

Matrix size (e.g. 128*128*31)	
Voxel size (e.g.2.0*2.0*2.0 mm^3)	
Reconstruction algorithm (e.g. OSEM)	
Smoothing filter and cut-off if used (e.g. Hanning, 0.5 Nyquist)	
Reconstruction algorithm parameters (number of iterations, subsets)	

Signed by person responsible for ensuring adherence to quality control procedures

Name: Date:

PHANTOM SCAN EVALUATION
(to be completed by Core Lab)

PET Centre:

Scanner Manufacturer and Model:

QC tests performed by:

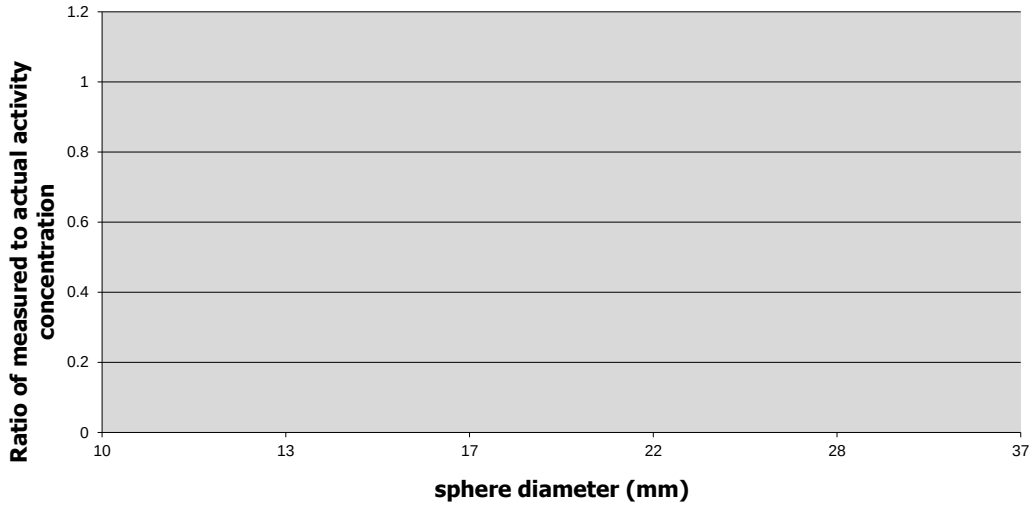
Date:

Qualitative Analysis:

Image Quality	Acceptable	Not acceptable
PET/CT alignment on core centre reporting system	Acceptable	Not acceptable
Comments		
Sphere activity concentration at scan start time:		MBq/ml
Background activity concentration at scan start time:		MBq/ml

	Activity Concentration		
	Measured (M)	**Actual (A)**	**Ratio**
Sphere diameter (mm)	**kBq/ml**	**kBq/ml**	M / A
37			
28			
22			
17			
10			
13			

A recovery curve should be generated from the tabulated data:



Average SUV for a large ROI positioned over the background:_____ (1 ± 0.1)

Recovery Curve:	Acceptable	Not acceptable

TEST PATIENT DATA FOR PET- CT SCAN - PATIENT 1

PET-CT Scan acquired at (PET Centre)

Patient's initials:

Date of PET-CT scan:

Time of administration of activity (hour:min)	
Activity at time of administration (MBq)	
Patient height (cm)	
Patient weight (kg)	
Patient fasting state (time last ate)	
Patient blood glucose	
Scanner sensitivity in units of Bq/ml (voxel value)	
Daily quality control result for the day of the scan	

	START TIME	NO. OF BED POSITIONS	DURATION PER BED POSITION	TOTAL SCAN DURATION
HALF BODY EMISSION SCAN				
HEAD & NECK SCAN (if acquired)				

Test data review (to be completed by Core Lab)

Comments

APPROVED	REJECTED

Name Date

Name Date

TEST PATIENT DATA FOR PET- CT SCAN - PATIENT 2

PET-CT Scan acquired at (PET Centre)

Patient's initials:

Date of PET-CT scan:

Time of administration of activity (hour:min)	
Activity at time of administration (MBq)	
Patient height (cm)	
Patient weight (kg)	
Patient fasting state (time last ate)	
Patient blood glucose	
Scanner sensitivity in units of Bq/ml (voxel value)	
Daily quality control result for the day of the scan	

	START TIME	NO. OF BED POSITIONS	DURATION PER BED POSITION	TOTAL SCAN DURATION
HALF BODY EMISSION SCAN				
HEAD & NECK SCAN (if acquired)				

Test data review (to be completed by Core Lab)

Comments

APPROVED	REJECTED

Name Date

Name Date

NOTIFICATION TO PET SCANNING FACILITY OF APPROVAL TO SCAN PATIENTS IN TRIAL

From:	
To:	PET Scanning Facility
Fax Number:	
To:	Haematology Trials Group
Fax Number:	+44 207 679 9861

Approved for trial

QC procedures	YES	NO
Scan acquisition and reconstruction parameters	YES	NO
Phantom data and patient test data	YES	NO
Data transfer	YES	NO

Name Date

Patient test data	YES	NO

Name 1 Date

Name 2 Date

The above named Centre has complied with the requirements for PET-CT scanning and is a recognised scanning facility in the trial. The Centre undertakes to notify the Core Lab immediately of any deviations in QC and scan acquisition or reconstruction parameters from those agreed.

A Randomised Phase III Trial to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin Lymphoma (RATHL)

REQUEST FOR PET- CT SCANS (pre-treatment) and 2 (post 2 cycles ABVD); both to be arranged at baseline

Patient details (attach label):

Patient's telephone number:	
Referring Consultant:	
Consultant telephone number:	
Consultant fax number:	
Hospital Address:	
Date registered into trial:	
Trial number:	
Please State	
Date Cycle 1 day 1 ABVD	
Intended date of Cycle 2 day 15 ABVD*	

*The second PET/CT scan will be arranged 9–13 days after this date.

FOLLOWING REGISTRATION, SEND THIS FORM TO THE PET SCANNING CENTRE OF YOUR CHOICE (LISTED IN SEPARATE APPENDIX) THE PET CENTRE MUST BE INFORMED PROMPTLY IF THERE ARE ANY DELAYS TO CHEMOTHERAPY

A Randomised Phase III Trial to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin Lymphoma (RATHL)

REQUEST FOR PET- CT SCAN 3
(for patients receiving treatment with BEACOPP-14 or Escalated BEACOPP having been PET positive after 2 cycles ABVD)

Patient details (attach label):

Patient's telephone number:	
Referring Consultant:	
Consultant telephone number:	
Consultant fax number:	
Hospital Address:	
Date registered into trial:	
Trial number:	
Please State	
Date cycle 1 day 1 BEACOPP-14/Escalated BEACOPP	
Intended date of Cycle 4 day 8 BEACOPP-14 or Cycle 3 day 8 escalated BEACOPP**	

* BEACOPP-14 - The PET/CT scan should be arranged 2–6 days after this date.
* Escalated BEACOPP – The PET/CT scan should be arranged 9-13 days after this date.

AT THE START OF TREATMENT (BEACOPP-14/Escalated BEACOPP), SEND THIS FORM TO THE PET SCANNING CENTRE OF YOUR CHOICE (LISTED IN SEPARATE APPENDIX) PET CENTRE MUST BE INFORMED PROMPTLY IF THERE ARE ANY DELAYS TO CHEMOTHERAPY

A Randomised Phase III Trial to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin Lymphoma (RATHL)

ACQUISITION DATA FOR PET- CT SCAN
(to be completed by PET scanning facility)

PET-CT Scan acquired at		(PET Centre)
Patient's initials:		
Patient's trial number:		
Referring Consultant:		
Consultant telephone number:		
Consultant fax number:		
Hospital Address:		
Date of PET-CT scan:		

Time of administration of activity (hour:min)	
Activity at time of administration (MBq)	
Site of tracer administration and state left or right	
Patient height (cm)	
Patient weight (kg)	
Patient fasting state (time last ate)	
Patient blood glucose	
Scanner sensitivity in units of Bq/ml (voxel value)	
Daily quality control result for the day of the scan	
Any deviations from the previously forwarded protocol?	
If yes, please specify	

	START TIME	NO. OF BED POSITIONS	DURATION PER BED POSITION	TOTAL SCAN DURATION
HALF BODY SCAN				
HEAD & NECK SCAN (if acquired)				

RESULT OF PET-CT SCAN according to 5 point scale:

1 no uptake
2 uptake ≤ mediastinum
3 uptake > mediastinum but ≤ liver

NOTE if mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver=score 2; lesion uptake equal to liver=score 3)

4 moderately increased uptake compared to liver at any site
5 markedly increased uptake compared to liver at any site

X new areas of uptake unlikely to be related to lymphoma

Local Report

Score: (Please circle)	1	2	3	4	5	X

Comments e.g. 'X' sites not related to lymphoma

Name Date

Signature

Central Report

Score: (Please circle)	1	2	3	4	5	X

Comments e.g. 'X' sites not related to lymphoma

Name 1 Date

Name 2 Date

Signatures

WHEN COMPLETED, SEND BOTH SHEETS WITH IMAGE DATA FILES (SEE PROTOCOL) TO NAMED PERSON AT CORE LAB AND RETAIN FIRST COPY FOR PET CENTRE RECORDS.

A Randomised Phase III Trial to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin Lymphoma (RATHL)

CENTRAL PET-CT SCAN REPORT FOLLOWING CENTRAL REVIEW

PET SCAN AFTER 2 CYCLES OF ABVD

Patient's initials:	_____
Patient's trial number:	
Referring Consultant:	
Consultant telephone number:	
Consultant fax number:	
Hospital Address:	
Date of PET-CT scan:	

The FDG-PET scan performed on (date) has been given a

Score: (Please circle)	1	2	3	4	5	X

by

1 (name)

2 (name)

following central review.

FAX TOP SHEET TO REFERRING CONSULTANTANDCOPY TO THE HAEMATOLOGY TRIALS GROUP (+44 207 679 9861) AND RETAIN SECOND COPY FOR CORE LAB RECORDS

A Randomised Phase III Trial to assess response adapted therapy using FDG-PET imaging in patients with newly diagnosed, advanced Hodgkin Lymphoma (RATHL)

CENTRAL PET-CT SCAN REPORT FOLLOWING CENTRAL REVIEW

PET SCAN AFTER 4 cycles of BEACOPP-14 or 3 cycles of BEACOPP-escalated (3rd PET SCAN)

Patient's initials:	_____
Patient's trial number:	
Referring Consultant:	
Consultant telephone number:	
Consultant fax number:	
Hospital Address:	
Date of PET-CT scan:	

The FDG-PET scan performed on (date) has been given a

Score: (Please circle)	1	2	3	4	5	X

by

1 (name)

2 (name)

following central review.

FAX TOP SHEET TO REFERRING CONSULTANT AND COPY TO THE HAEMATOLOGY TRIALS GROUP (+44 207 679 9861) AND RETAIN SECOND COPY FOR CORE LAB RECORDS

SUV ANALYSIS

The study will rely on visual interpretation only. However data will be collected for post hoc analysis to determine whether visual interpretation can be refined and semi-quantitative measures used to subgroup patients further into 'tighter' quantitative response categories which may have prognostic value. A scheme for analysis of semi-quantitative data is suggested below.

The 'hottest' lesions at staging will be chosen for SUV analysis but if subsequently the response scan shows residual activity at sites different from the 'hottest' lesions at staging, these sites will be used as the index lesions instead. . Uptake in up to four lesions will be documented. The maximum SUV within the lesion will be calculated using decay corrected administered dose and body weight. The maximum SUV will be selected using a region of interest placed on the axial PET slice with the highest uptake. The CT diameter of the mass will be recorded on the axial slice with the greatest CT diameter. Note the PET and CT axial slices may not match as the maximum SUV may occur within the lesion in a different axial plane to the maximum size on CT.

Staging scan

Index lesion	Site e.g. left supraclavicular	SUV max	PET axial slice	CT max transverse diameter (mm)	CT axial slice
1					
2					
3					
4					

Response scan after primary chemotherapy

Correlate with staging scan index lesions and note any additional lesions with higher uptake

Index lesion	Site e.g. left supraclavicular	SUV max	PET axial slice	CT max transverse diameter (mm)	CT axial slice
1					
2					
3					
4					
5					
6					
7					
8					

Appendix 6: PROTOCOL VERSION HISTORY

Protocol:		Amendments:
Version no.	**Date**	**Summary of main changes from previous version.**
5.0	10.02.2012	• Protocol restructured in line with current UCL CTC protocol template • Changes to trial contacts – addition of details of TMG • Further information added to study synopsis (section 1.1) • Site selection criteria (section 3) expanded • Addition of informed consent section (section 4) • Addition of pregnancy test for women of childbearing potential to baseline investigations (section 5.1) • Minor change of inclusion criterion 12 from "Access to PET-CT scanning" to "Access to an approved PET-CT scanning facility" (section 5.3.1) • Change of exclusion criterion 8 from "Previous history of active malignant disease other than fully excised basal or squamous cell carcinoma of the skin or carcinoma in situ of the uterine cervix in the past 10 years" to "Concurrent active malignancy other than fully excised non melanoma skin cancer or squamous cell carcinoma of the cervix. Subjects with previous malignancies are eligible provided they have been disease free for at least 5 years". (section 5.3.2) • Change of arrangements for pathology specimens – now being sent directly to the HMDS rather than to UCL CTC (section 5.4) • Addition of guidance on contraception and fertility (section 5.5) • Further detail about registration procedures (section 6) • Clarifications about dose adjustments and dose capping; addition of details regarding administration of Natulan (to be used where UK licensed procarbazine is unavailable in the UK); further information about pharmacy responsibilities (section 7) • Clarification regarding requirement for a 3 month post-treatment CT scan (section 8.3) • PV section (section 11) amended – now collecting all AEs, rather than just grade 3 & 4; exemptions to SAE reporting expanded; guidance regarding overdoses added; further details added on processing of SAEs & SUSARs at UCL CTC; requirement to submit DSURs • Addition of information about incident reporting and serious breaches (section 12) monitoring and oversight (section 13), • Sponsorship and Indemnity section updated to reflect the Sponsor's current arrangements (section 18) • Publication policy expanded (section 20) • Further references added (section 21) • List of abbreviations added (appendix 1) • Expected AEs section amended to reflect AEs expected for the ABVD, AVD & BEACOPP regimens based on the extant clinical literature (appendix 3) • Addition of pregnancy test to schedule of investigations (appendix 4) • Change to PET scanning protocols relating to uptake time (appendix 5 – detailed scanning protocol) • Corrections of minor typographical errors
4.0	30.11.2009	Inclusion criterion number 9 relating to pulmonary function test removed, Assessment times changed for bloods and other investigations. A number of other changes.
3.1	10.10.2008	PIS, GP Letter and consent form removed from protocol. Number of other minor changes.
3.0	18.09.2008	Timing of PET scanning changed, timing of the response assessment clarified and a number of other administrative changes.
2.4	17.03.2008	First Approved Protocol