Protocol for a sub-study of the R-CHOP-21 v R-CHOP-14 trial

Blinded evaluation of prognostic value of FDG-PET after 2 cycles of chemotherapy in Diffuse Large B-cell Non-Hodgkin's Lymphoma

Short title: PET after 2 cycles

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Approved by Chief Investigator	**Dr George Mikhaeel**
Signature	
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A trial developed by the National Cancer Research Institute Lymphoma Study Group and adopted by the National Cancer Research Network

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Section 1: PET substudy Working Group

Queries should be directed to an appropriate member of the Trial Working Group:

Principal Investigator of PET substudy:

Dr George Mikhaeel
Department of Oncology
St Thomas' Hospital
Lambeth Palace Road
London SE1 7EH
Tel: 020 7188 4219
Fax: 020 7928 7963
Email:
george.mikhaeel@gstt.nhs.uk

PET Co-investigator:

Dr Mike O'Doherty
Clinical PET Centre
St Thomas' Hospital
Lambeth Palace Road
London SE1 7EH
Tel: 020 7188 4988
Fax: 020 7620 0790
Email:
mike.o'doherty@gstt.nhs.uk

Chief Investigator of main trial (R-CHOP 14 v 21)

Professor David Cunningham
Department of Oncology
Royal Marsden Hospital
Downs Road
Sutton, Surrey
SM2 5PT
Tel: 020 8661 3156
Fax: 020 8643 9414
Email:
david.cunningham@icr.ac.uk

Trial Coordinator:

Mr Paul Mouncey
Lymphoma Trials Office
CRUK and UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ
Tel: 020 7679 9876
Fax: 020 7679 9861
Email:
p.mouncey@ctc.ucl.ac.uk

Data Management:

Miss Rachel Haley
Lymphoma Trials Office
CRUK and UCL Cancer Trials Centre
90 Tottenham Court Road
London W1T 4TJ
Tel: 020 7679 9867
Fax: 020 7679 9861
Email:
r.haley@ctc.ucl.ac.uk

Statistician:

Dr Wendi Qian
MRC Clinical Trials Unit
222 Euston Road
London NW1 2DA
Tel: 020 7670 4705
Fax: 020 7679 9861
Email:
wendi.qian@ctu.mrc.ac.uk

The protocol may be revised periodically. If so participating centres will be informed. New centres are advised to check with the Lymphoma Trials Office that they have the current version of the protocol.

Section 2: Background

Diffuse large B-cell Lymphoma (DLBCL) is the most common subtype of high-grade non-Hodgkin-lymphoma (NHL). Most patients respond to conventional chemotherapy but only just over a half of patients is cured with standard regimes e.g. R-CHOP. Salvage high-dose chemotherapy with haematopoietic stem cell support improves the outcome of primary refractory or relapsed disease. Prognosis can be estimated by international prognostic index (IPI) however, the routine upfront use of high-dose chemotherapy in poor prognosis patients is controversial and has not been consistently proven to improve outcome. The selection of patients for such treatment intensification may be more effective if based on the response of the individual patient to treatment as opposed to pre-treatment IPI.

Positron emission tomography with 2-[18F] fluoro-2-deoxy-D-glucose (FDG-PET) performed early during the course of chemotherapy has in recent years been recognized as a strong predictor of outcome in high-grade NHL. Published data suggest that complete response (CR) is readily evident on FDG-PET after 2-3 cycles and that such early CR on FDG-PET confers a favourable prognosis. *Hoekstra et al*. presented the first report suggesting a role for FDG in the early monitoring of lymphoma Treatment in 1993[1]. 13 NHL patients were examined after two courses of chemotherapy with a planar gamma camera. Negative scans preceded complete remission in 7/13 patients and abnormal uptake preceded treatment failure or death in four patients. A subsequent investigation by *Mikhaeel et al* demonstrated the prognostic properties of an early interim FDG-PET after 2-3 cycles of chemotherapy on 23 HG-NHL patients[2]. In their study of 28 heterogeneous NHL patients, Jerusalem et al. found significantly better short-term disease-free survival among the patients who were FDG-PET-negative after 2-5 cycles of chemotherapy[3]. These studies indicate a strong predictive value of an interim FDG-PET, but they are based on small numbers and short follow-up.

More recently 3 large studies have been published addressing this question. In a Belgian series[4], 70 patients with aggressive NHL underwent a PET at mid-treatment. 33 patients were not in complete response (CR) and none of them achieved a durable CR, compared to 37 Patients with negative scans of which 31 remained in CR with a median follow-up of 1107 days. PET was a stronger prognostic predictor for progression-free-survival (PFS) and OS than IPI. A French study[5] on 90 patients with aggressive NHL, who had PET after 2 cycles, showed similar results. PET was negative in 54 patients and positive in 36 patients, with 2-year PFS of 82% and 43% ($p<0.0001$) and 2-year OS of 90% and 60% ($p<0.006$), respectively. The largest series is from the UK[6] and includes 121 patients with aggressive NHL and median follow up of 28.5 months (range 3-101), confirms that response on PET after 2-3 cycles strongly predicts PFS and OS. 50 FDG-PET scans were negative, 19 scans showed minimal residual uptake (MRU), and 52 scans were positive. The estimated 5-year PFS was 88.8% for the PET-negative group, 59.3% for the

MRU group, and 16.2% for the PET-positive group. Kaplan-Meier analyses showed strong associations between FDG-PET results and PFS ($p < 0.0001$) and OS ($p < 0.01$).

Taken together, the above evidence suggests that an early repeat FDG-PET during treatment is an accurate predictor of PFS and OS and is stronger than other known prognostic factors. FDG-PET offers a **more individualised** prognostic tool (based on response to treatment) allowing **early** identification of high-risk patient, who are unlikely to be cured by conventional therapy, for more intensive treatment.

This approach of Response-adapted therapy will need to be tested in a randomised controlled trial (RCT). It is crucial to validate the above data before using PET in an RCT. In the studies mentioned above, neither the clinicians were blinded to PET result, nor were the nuclear medicine physicians always completely blinded to clinical response, potentially biasing the results. Patients were also treated with different chemotherapy regimens (mostly without Rituximab) and treatment decisions were made according to the discretion of treating clinician. The prognosis of different PET groups varied between studies. If PET is to be used for guiding treatment decisions in the future, an accurate estimate of prognosis of different PET groups, without any confounding factors, is needed.
The proposed study will avoid these biases and also ensure that all patients will be treated in homogenous way according to one protocol using R-CHOP (the current international standard of care) in a controlled trial setting, where PET scans will not be used for treatment decisions.

2.1 RATIONALE OF THE STUDY

The study aims to confirm the prognostic value of FDG-PET after 2 cycles of chemotherapy in a **prospective controlled trial**, where all patients are treated uniformly according to the **same protocol**, which depends on CT for response evaluation. Clinicians will be blind to the result of PET after 2 cycles and all treatment decisions will be based on the agreed response criteria regardless of PET scan outcome.
This investigation will be conducted as a sub-study within NCRI "R-CHOP 14 v 21" trial. The results will provide the strongest evidence to date on the prognostic value of PET after 2 cycles. If proved useful on this evidence, it can be used in the future to select non-responding patients, early in their treatment, for alternative therapy (e.g. stem cell transplantation).
The study will also offer a unique opportunity to evaluate a **quantitative response system** using percentage reduction in "Standard Uptake Value" [SUV] (see below).

2.2 STUDY OBJECTIVE

To evaluate the prognostic value of FDG-PET after 2 cycles of chemotherapy in DLBCL, specifically answering the following questions:

- Does FDG-PET after 2 cycles of chemotherapy predict the **final outcome** of treatment (i.e. degree of response)?
- Does early complete response on PET after 2 cycles predict for **better prognosis** (and does the lack of complete response predict for poor prognosis)?
- What is the **magnitude of difference** in Failure-free Survival between PET positive and PET negative patients?
- Can response be **quantitatively** assessed with PET? And does the "degree of response" (measured by percentage reduction in SUV) divide the PET positive group into distinct prognostic groups?

The response on PET will be correlated to:

Primary Outcome Measure:

Failure free survival at 2 years

Secondary Outcome Measures:

Complete response rate
Overall survival

Section 3: Study Details

3.1 STUDY DESIGN

- All patients entered in the study will have a pre-treatment FDG-PET scan and a repeat FDG-PET scan after 2 cycles of chemotherapy.
- Scans will be archived centrally and treating clinicians will be blinded to the scans' findings.
- Patients will be treated according to the "R-CHOP 14 v 21 trial" protocol, with a repeat CT scanning after 4 cycles of chemotherapy. Response will be assessed in accordance with the International Workshop Standardised Response Criteria for Non-Hodgkin's Lymphoma.
- Nuclear Medicine physicians reporting the PET scans will be blinded to the outcome of treatment.
- The PET scans will be reported in batches and archived centrally. Analysis of data will be performed after completion of recruitment.
- The result of the PET scan will be correlated to treatment outcome, i.e. FFS at 2-years and CR rate.

3.2 ELIGIBILITY CRITERIA

Inclusion criteria:
All patients entered in NCRI **"R-CHOP-14 v 21"-trial,** with access to PET scanning will be eligible, if they have a positive pre-treatment FDG-PET (i.e. showing abnormal uptake in disease sites)

Exclusion Criteria:
Patients with a negative pre-treatment PET scan.

3.3 PET SCANNING

3.3.1 Timing

Baseline PET scan:
All patients should have a pre-treatment FDG-PET scan as a baseline study to be compared with subsequent scans to assess response. This should be performed within **2 week** of starting treatment. The PET scan should be performed either before or 3-4 days after a CT scan with bowel contrast.
Clinicians participating in the study will request an FDG-PET scan from the participating centres and if unable to get these performed within 1 week; the trial centre will locate a centre that can perform the initial scan. The second scan must be performed at the same centre as the baseline scan.

PET scan after 2 cycles:
A second PET scan will be performed **the week before** the **third cycle** of chemotherapy in both arms of the main study (i.e. R-CHOP-14 and R-CHOP-21 arms). It is advisable to book the second PET at the time of starting treatment, to ensure appropriate timing in the week before the 3rd cycle.

3.3.2 Scanning Facilities

- Only full-ring 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 sites, and an agreed file naming convention adhered to
- A named person at the scanning facility, who will ensure that correct and agreed acquisition and data transfer protocols are adhered to, must be designated.

The following MUST ALL be completed and approved by the central reporting facility before any patients are scanned:

- The scanner specification (manufacturer, model, installation date), routine scanner QC procedure, details of the proposed acquisition protocol and details of the contact person must be forwarded to PET centre at Guy's & St Thomas' Hospital.
- The scanner quality-control test must be completed and passed.
- It must be demonstrated that standard uptake values can be reliably determined from the PET images both at the scanning facility and at the central reporting facility.
- It must be demonstrated that anonymised PET and CT images can be transferred from the scanning facility to the central reporting facility, and a file naming convention established

3.3.3 Scanning Protocol

Patient preparation

1. Patients must be asked to fast for 6 hours prior to the scan
2. The patients should be scanned with arms above the head for the body scan and by the side for head and neck scan

Detailed scanning protocol

1. Administer 350 - 400 MBq ^{18}FDG
2. ***Emission part of the scan must start at 90 minutes after injection***
3. Perform attenuation corrected 'half-body' scan to cover the area from the base of the brain to mid-thigh using the CT of the PET-CT scanner.
4. Perform head and neck scan if required

Acquisition should be performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, arms up/down, 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 forwarded to Guy's & St. Thomas' PET centre prior to the start of the study.

3.3.4 Radiation Dosimetry

The effective dose associated with an administration of 400 MBq 18-FDG is 10.0 mSv (ARSAC Notes for Guidance 1998). The target organ is the bladder wall, which will receive 68.0 mGy (ICRP Publication 53). The CT attenuation correction using 80 mA and 150 kV will be approximately 8 mSv for the half body.

3.3.5 ARSAC Approval

An ARSAC research certificate must be obtained individually for each participating PET centre prior to starting the study. A template application form will be made available.

3.3.6 Information to be recorded on each patient

For each patient study data acquisition information and patient information must be recorded on the PET scan report form (Appendix 3) and forwarded to Guy's & St. Thomas' PET centre, together with the staging CT scan report.

3.3.7 Image Data Transfer

Image data must be transferred to St Thomas', in a pre-agreed anonymous format, at the same time as the completed PET scan report form.

The following files are required

- Attenuation corrected half body images
- Non-attenuation corrected half body images
- Half body CT scan
- Attenuation corrected local view (if performed)
- Non-attenuation corrected local view (if performed)
- Local view transmission image (if performed)

Projection images (MIPs) are not required

All files must be unambiguously named using a pre-arranged filename convention.

3.3.8 Scan Reporting

PET scans will be reported and reviewed by 3 Nuclear Medicine physicians, Dr M O'Doherty, Dr SF Barrington and Dr T Nunan, blinded to the patient's outcome. Each scan will be reported by 2 physicians. Any differences will be resolved by consensus or a third read by one of the three clinicians. The scans will be reported in batches and reports will be archived centrally until final analysis.

3.3.9 Response categories

The post-cycle 2 PET scan will be allocated to one of the following categories:

1. Negative: complete disappearance of all abnormal uptake on the pre-treatment PET

2. Positive: include

2a. Minimal Residual Uptake (MRU): Disappearance of most abnormal uptake, but residual low-grade uptake in sites of previous disease, just above the background activity.

2b. Partial response: Reduction in the abnormal uptake, but significant residual activity.

2c. Stable: No significant change.

2d. Progression: Increase in abnormal uptake &/or appearance of new sites.

The main analysis will compare 2 groups; namely negative and positive.

Standard uptake values (SUVs) will be used to quantify tracer uptake, and response to therapy will be determined by the percentage change in SUV for scans acquired before and after therapy. The percentage change in SUV will be correlated with actual prognosis to test the possibility of defining "quantitative response categories" which have prognostic value.

Section 4: Outcome Measures

The following outcome measures will be compared in the response categories:

Failure free survival

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

Complete response rate

Response will be assessed in accordance with the International Workshop Standardised Response Criteria for Non-Hodgkin's Lymphoma (as per main trial protocol).

Section 5: Statistical Considerations

Previous studies[4-6] showed that 41–60% of patients will have a negative PET scan after 2-3 cycles of chemotherapy. Mikhaeel et al[5] showed 2-year progression-free survival of **93**%, 59.3% and **30.3**% for PET positive, MRU and PET negative groups respectively. Haioun et al[6] showed 2-year event-free survival of **82**% and **43**% for PET positive and PET negative groups respectively.
Assuming that about 50% of patients will have a negative PET scan after 2 cycles and to detect a much smaller difference (**25%**) in Failure Free Survival (FFS) at 2-years between PET negative & positive groups, with 5% type I error and 90% power, **200 patients** will be required.

25% difference in FFS is considered to be the minimal clinically significant difference.

Details of Calculation for 25% difference:
2y FFS for PET negative/positive of 80%/55%: events needed=47, patients needed=191
2y FFS for PET negative/positive of 75%/50%: events needed=60, patients needed=209

Data from this sub-study will be reviewed by the Independent Data Monitoring Committee (IDMC) one year after the study commences. The IDMC will advise about the continuation of the study. The study will be stopped if the there is reliable evidence that the above difference has been achieved early.

Section 6: References

1. Hoekstra OS, Ossenkoppele GJ, Golding R, et al: Early treatment response in malignant lymphoma, as determined by planar fluorine-18-fluorodeoxyglucose scintigraphy. J Nucl Med 34:1706-1710, 1993

2. Mikhaeel NG, Timothy AR, O'Doherty MJ, et al: 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. Leuk Lymphoma 39:543-553, 2000

3. Jerusalem G, Beguin Y, Fassotte MF, et al: Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. Haematologica 85:613-618, 2000

4. Spaepen K, Stroobants S, Dupont P, et al: Early restaging positron emission tomography with (18)F-fluorodeoxyglucose predicts outcome in patients with aggressive non-Hodgkin's lymphoma. Ann Oncol 13:1356-1363, 2002

5. Haioun C, Itti E, Rahmouni A, et al : [18F]fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) in aggressive lymphoma: an early prognostic tool for predicting patient outcome. Blood 2005; 106:1376-81 (published online May 2005)

6. Mikhaeel NG, Hutchings M, Fields P, et al: FDG-PET after 2-3 of chemotherapy predicts progression-free and overall survival in high-grade Non-Hodgkin Lymphoma. Ann Oncol. 2005 Sep;16(9):1514-23. Epub 2005 Jun 24

APPENDIX 1: PATIENT INFORMATION SHEET

Study title: Blinded evaluation of prognostic value of FDG-PET after 2 cycles of chemotherapy

Study acronym: PET after 2 cycles

PATIENT INFORMATION SHEET

You have agreed to take part in the R-CHOP 14 v 21 study. Your are now invited to take part in the PET substudy. Before you decide if you would like to take part, it is important that you understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP, if you wish. If you decide to enter the study your GP will be made aware of this. Ask us if there is anything that is not clear or if you would like more information.

Information regarding cancer, clinical trials and treatment is available through the CancerHelp UK website, www.cancerhelp.org.uk and the CancerBACUP website, www.cancerbackup.org.uk. CancerBACUP and the Lymphoma Association also publish leaflets for patients with lymphoma.).

What is the purpose of the study?

You have a condition called non-Hodgkin's lymphoma. In particular, you have a subtype of non-Hodgkin's lymphoma called diffuse large B cell non-Hodgkin's lymphoma. You are taking part in the main study, where you will receive chemotherapy with a combination of drugs called R-CHOP, given either every 14 or 21 days.

In the main study, you will have a second CT (computed tomography) scan after 4 cycles of treatment, to find out if the treatment is working and the lymphoma cancer is responding to it. This is the standard way of assessing response to treatment in Lymphomas.

PET (Positron Emission Tomography) is a new imaging (scanning) technique that has proven useful in the treatment of Lymphomas. PET works in a different way to CT. CT shows lymphoma by the presence of enlarged lymph glands or organs, or by change in appearance of organs (e.g. liver and spleen). It does not tell us if the enlarged lymph glands definitely have lymphoma or not. PET scanning, works by showing the metabolic activity of the tissues (based on their glucose uptake). Lymphoma cells usually have a high metabolism (i.e. glucose uptake), compared to normal tissues. PET scan is able to show response to treatment earlier than CT, where changes indicating response take longer time to appear.

In previous research, a repeat PET after only 2 cycles of chemotherapy was able to show response early and the findings of PET scan was predictive of the chances of cure. If this is proven in this study, PET could help us in the future to change ineffective treatment early, so avoiding unnecessary toxicity and hopefully curing more people.

We would like to find out if the PET can reliably assess response to treatment early during treatment and hence predict the prognosis. To do this we need to evaluate PET on patients treated the same way according to one protocol (the main study protocol).

Why have I been chosen?

Patients participating in the main study, who have access to PET scanning are all invited to participate in the PET substudy.

Do I have to take part?

Your participation in this trial is entirely voluntary. If you decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw or a decision not to take part will not affect the standard of the care you receive.

What will happen to me during the study?

If you are willing to participate in the PET trial, you will be assessed by your doctor to ensure you are suitable to take part. You will be treated in the same away outlined in the main study. The only difference will be that you will have an additional PET scan, before you start treatment and a second PET scan before the 3rd cycle of chemotherapy, whether it is 14- or 21-day cycles. The scan results will not affect your treatment. All treatment decisions will be based on the standard CT scan. The PET scan result will be kept confidential to be analysed at the end of the study.

Are there any side effects associated with the PET scan?

There is a small radiation exposure dose involved in the PET scan. This is unlikely to have any short or long-term effects on your health.

You will need to be fasting for 6 hours before the PET scan.

What are the possible benefits of taking part?

The information we get from the PET study may help us to improve the future treatment of patients like you with diffuse large B cell non-Hodgkin's lymphoma.

Will information about me in this study be kept confidential?

All information which is collected about you during the course of this study will be kept strictly confidential. Any information about you which leaves the hospital will have your name and address removed, so you cannot be identified from it. We may need to obtain information from the Office of National Statistics.

Who is sponsoring and organising the research?

This study is organised on behalf of the National Cancer Research Institute and is co-ordinated by the Lymphoma Trials Office.

What will happen to the results of the study?
Results will be analysed by the Lymphoma Trials Office. They will be presented at haematological and oncological meetings and published in associated journals.

What if I do not wish to take part or change my mind?

The study is voluntary so that you should not feel under any pressure to enter. If you decide to take part you are free to withdraw at any time. In either case, you do not have to give a reason for your decision and this will not prejudice your future medical care. **If you decide not to participate in the PET study, you can still participate in the main study.**

There is no facility for payment of clinicians or patients or travel expenses.

If you do decide to take part in this research study, you will be asked to sign a consent form. You have 7 days to decide. Should you have any further queries regarding this study or about any of the treatments described above:

Please contact _____
Name and Title

APPENDIX 2: PATIENT CONSENT FORM - PART III (PET study)

Study title: A multicentre randomised clinical trial comparing rituximab with CHOP given 14 days and rituximab with CHOP given every 21 days for the treatment of patients with newly diagnosed diffuse large B cell non-Hodgkin's lymphoma

Substudy title: Blinded evaluation of prognostic value of FDG-PET after 2 cycles of chemotherapy in Diffuse Large B-cell Non-Hodgkin's Lymphoma

PATIENT CONSENT FORM PART III* (please read carefully)

Name of Researcher: _____

Please initial

I confirm that I have read and understand the information dated 26 July 07(version 2.0) for the above study and have had an opportunity to ask questions.	
I understand that my participation in this study is voluntary and that I am free to withdraw at any time without giving a reason, without my medical care or legal rights being affected.	
I understand that the PET scan results will be anonymised, stored and analysed separately for the whole study. I understand that this will be linked to the trial data through the unique trial number and no other personal data will be held.	
I agree to take part in the PET study.	

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent (if different from researcher)	Date	Signature
_____	_____	_____
Name of Researcher	Date	Signature

* Three copies required: one each for the patient, researcher and hospital case notes

APPENDIX 3: PET scan report form

FDG-PET Scan report from …… **(PET Centre)**

Patient's initials:

Patient's trial number:

Referring Consultant: ……

Consultant telephone number: ……

Consultant fax number: ……

Hospital address: ……

……

Date of PET scan:

Time of administration of activity (hour:min)	
Activity at time of administration (MBq)	
Emission scan start time (hour:min)	
Patient height (cm)	
Patient weight (kg)	
Patient fasting state (time last ate)	
Patient blood glucose (units)	
Daily quality control result for the day of the scan	
Any deviations from the previously forwarded protocol?	
If yes, please specify	

Result of PET scan *

Whole Body Scan Overall

Name: ……

Signature ……...

Date: ……

*1 Negative 2 Positive: 2a=MRU, 2b= partial response, 2c= stable, 2d= progression

When completed, send the top sheet with image data files (see protocol) to Dr M O'Doherty, St Thomas' Hospital, London SE1 7EH and retain first copy for PET centre records.

APPENDIX 4: PET centres in trial

Centre	Contact
Cheltenham Cheltenham Imaging Centre Linton House Clinic Thirlestain Road Cheltenham, Glos GL53 7AS	Nigel Benatar Tel: 01242 535923 Email: nigel@cobaltappeal.com
Mount Vernon Paul Strickland Scanner Centre Mount Vernon Hospital Rickmansworth Road Northwood, London HA6 2RN	John Lowe Tel 01923 844045 Email: john.lowe@paulstrickland-scannercentre.org.uk
Nottingham City Hospital Campus Nottingham University Hospital NHS Trust Hucknal Rd Nottingham, NG5 1PB	David Griffiths Tel: 0115 993 6624 Email: david.griffiths@listerinhealth.com
St Thomas' Hospital The Clinical PET Centre Lambeth Wing St Thomas' Hospital London, SE1 7EH	Margaret Dakin Tel: 0207 188 1494 Email: margaret.dakin@kcl.ac.uk
UCH Institute of Nuclear Medicine University College Hospital 235 Euston Road London, NW1 2BU	John Dickson Email: John.Dickson@uclh.nhs.uk Tel: + 44 845 155 5000 Ext 70523 Fax: + 44 20 7637 0578