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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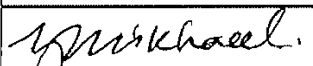
Signature	
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A trial developed by the National Cancer Research Institute Lymphoma Study Group and adopted by the National Cancer Research Network

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The protocol may be revised periodically. If so participating centres will be informed. New centres are advised to check with the Haematology Trials Group 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.

The response on post-cycle 2 PET will be also assessed according the new Deauville Crieteria intoduced by The first International Workshop on Interim PET in Lymphoma, Deauville, France, 2009 (Leuk Lymphoma. 2009 Aug;50(8):1257-60). The scans will be scored 1-5 as follows:
Score 1: No abnormal residual uptake.
Score 2: Residual uptake ≤ mediastinum.
Score 3: Residual uptake > mediastinum but ≤ liver
Score 4: Moderately increased uptake > liver
Score 5: Markedly increased uptake > liver and/or new lesions
Score X: new areas of uptake unlikely to be related to lymphoma

Comparison of the 2 scoring systems will also be conducted and the analysis will aim to find the best fit of classifying negative and positve scans in predicting prognosis.

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** with an evaluable PET scan after 2 cycles of treatment will be required.

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

<u>Details of Calculation for 25% difference:</u>
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: 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 2: PET centres in trial (up to date 26mar10)

Centre	Contact
Aberdeen Royal Infirmary	Fergus Mckiddie
Nuclear Medicine Dept Aberdeen Royal Infirmary Foresterhill Aberdeen AB25 2ZD	Tel. +44 (0)1224 552239 Email: f.mckiddie@abdn.ac.uk
Birmingham	Lee Jenkins
Queen Elizabeth Hospital Birmingham	Tel: 0121 627 2389 Email: lee.Jenkins@uhb.nhs.uk
Cheltenham	Nigel Benatar
Cheltenham Imaging Centre Linton House Clinic Thirlestain Road Cheltenham, Glos GL53 7AS	Tel: 01242 535923 Email: nigel@cobaltappeal.com
Christie PET Centre	David Ashworth
North Western Medical Physics Christie Hospital NHS Foundation Trust Manchester, M20 4BX	Tel: 0161 446 3906 Email: david.ashworth@physics.cr.man.ac.uk Peter Julyan Tel: 0161 446 3078 Email: peter.julyan@physics.cr.man.ac.uk
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Paul Strickland Scanner Centre Mount Vernon Hospital Rickmansworth Road Northwood, London HA6 2RN	Tel 01923 844045 Email: john.lowe@paulstrickland-scannercentre.org.uk
Nottingham	Charnie Kalirai
City Hospital Campus Nottingham University Hospital NHS Trust Hucknal Rd Nottingham, NG5 1PB	Tel: 0115 9691169 x55867 Email: charnie.kalirai@nuh.nhs.uk

Royal Preston	Angela Meadows Tel: 01772 524 100 Email: a.meadows@alliance.co.uk
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Wolfson Molecular Imaging Centre	Peter Julyan
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