

A phase II study VEPEMB in patients with Hodgkin's Lymphoma aged \geq 60 years.

Chief Investigator

Stephen J Proctor, Professor of Haematological Medicine, Haematological Sciences, School of Clinical & Laboratory Sciences, Leech Building, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH.

Phone: 0191 222 7791, Fax: 0191 222 5524, e-mail: s.j.proctor@ncl.ac.uk.

DATE :

Professor Stephen John Proctor

Principal Investigators

Penelope R. A. Taylor, Associate Specialist, Haematological Sciences, School of Clinical & Laboratory Sciences, Leech Building, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH.

Helen H Lucraft, Clinical Oncologist, NCCT, Newcastle upon Tyne, NE4 6BE.

Katrina M Wood, Consultant Pathologist, Department of Pathology, Royal Victoria Infirmary, Department of Haematology, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP.

John Goodlad, Consultant Pathologist, Highland Area Laboratory, Raigmore Hospital, Inverness, IV2 3UJ.

Study Statistician

Professor Robin Prescott, Director, Medical Statistics Unit, (R739), University of Edinburgh Medical School, Teviot Place, Edinburgh, EH8 9AG.

CONTENTS

1. Introduction	3
2. Study Outline	4
3. Objectives of the study	5
4. Eligibility	8
5. Pre Registration Investigations	9
6. Registration and Randomisation	10
7. Plan of Treatment	11
8. Other treatment issues	14
9. Evaluation of response	15
10. Follow up	16
11. Data collection/form completion	17
12. Endpoints	18
13. Statistical considerations	19
14. Ethical Considerations	21
15. Publication	22
16. References	23

Appendices

1. Definition of a fragile patient
2. Definition of geriatric syndrome
3. Criteria for the evaluation of performance status
4. Co-morbidity scale
5. ADL scale
6. IADL scale
7. Calculation of Hasenclever prognostic index
8. Therapy allocation form
9. Patient data forms
10. Common toxicity criteria
11. Quality of Life Assessments
12. Patient Information Sheet and Consent Forms
13. GP letter

1. Introduction

Hodgkin Lymphoma (HL) is a rare malignancy accounting for 1 in 4 cases of lymphoma. It is considered to have a favourable prognosis with recent improvements in treatment (1,2,3). However, outcome in older patients, who account for 20% of cases has not improved (4,5) and this is because of both the impact of comorbidity and the fact that older patients cannot tolerate the intensive therapies that have led to improvement in outcome in younger patients (5, 6, 7, 8).

Most studies of outcome in HL in older patients are retrospective or observational (4,5,6,7,8). They suggest older patients with HL have a different distribution of histological subtypes, and that Epstein Barr Virus (EBV) positivity of tumours predicts for poorer prognosis (5,9). There is also a suggestion that fewer older patients receive adequate treatment which may contribute to survival differences. It has been suggested that once older patients achieve a complete remission they are no more likely to relapse than younger patients.

Misdiagnosis of HL is more common in older patients and central histological review will be a requirement of the present study (9). The impact of EBV status of the Reed Sternberg cells will be assessed, as two preliminary reports (5,6) suggest this might have an impact on prognosis. 10mls of serum will be collected from all patients and stored in aliquots so that a full panel of serological prognostic factors (sCD 30 etc) can be assessed.

The gold standard of treatment for HL is Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD) (10) but this is rarely given without treatment delays in elderly patients. In an effort to improve results by minimising toxicities, specific regimens for the elderly have been introduced. Chlorambucil, Vinblastine, Procarbazine / Cyclophosphamide, Etoposide, Bleomycin (CVP/CEB) (11) and Prednisolone, Chlorambucil, Oncovin (Vincristine), Mitoxantrone, Etoposide (PCOME) (5) were well tolerated but results are disappointing. More recently the Italian Group have piloted a novel regimen Vinblastine, Endoxana (Cyclophosphamide), Procarbazine, Prednisolone, Etoposide, Mitoxantrone, Bleomycin (VEPEMB) (12) which they found gave similar results to ABVD when compared to historical cases but was better tolerated.

The data from the preliminary VEPEMB study demonstrated the prognostic importance of comorbidity. Sub division by age (66-70, 71-75 and >75) predicted for outcome but the need for a methodology for assessing the fragility of the aged so as to objectively assess those who would be unable to tolerate aggressive treatment became apparent.

The complexity of obtaining data from the numerous questions which are needed for a "comprehensive geriatric assessment" has led to a move within oncology for a simplified system. Assessment of patients using "activities of daily living score" (ADL) (13) and instrumental activities of daily living (IADL) (14) correlates well with the complex "sickness impact profile" (16) and would seem suitable for use in a prospective multicentre study as a reproducible comorbidity assessment.

In the present study, patients who are deemed 'fragile' will be excluded from the phase II study but it is hoped to assess prospectively if it is possible to predict which patients considered "not fragile" are unable to tolerate chemotherapy and for whom other treatment options would be more suitable (15).

Various prognostic indices are in use in younger patients with HL, (17,18) but these evolved from data on younger patients and have not been validated in the older age groups. The Hasenclever index (18) is in general use for deciding treatment in trials in younger patients and, whilst it will not be used for stratification in the current study, its applicability will be assessed.

In brief, this study will evaluate whether a simplified, multidimensional fragility score which is easy to apply can predict which patients can tolerate treatment in a study of the efficacy of reduced intensity treatment (VEPEMB) in older patients.

2. Study Outline

Eligible patients who are considered fit for protocol chemotherapy will be asked to give their consent:

- a. for tumour tissue to be reviewed centrally.
- b. to be treated according to the protocol regimen to which they are allocated.
- c. to allow data on their treatment and outcome to be recorded and analysed.

Patients with HL who are otherwise eligible but who are unfit or non-consenting for protocol chemotherapy but who are willing for their tissue to be reviewed and basic data recorded (i.e. they consent to parts A and C above) should also be registered, and will contribute only to the data collection and pathology study.

3. Study Objectives

Clinical

- To evaluate the efficacy and toxicity of VEPEMB in a phase II study in older patients with HL.
- A number of older patients with HL fail to enter clinical trials as they are “not fit” for multiple drug chemotherapy. This study will aim to include all pathologically eligible patients in participating centres in order to provide a clearer overall clinical picture of this disease, whether or not they undergo protocol chemotherapy.

Pathological

Central Histological Review

Diagnostic material from all patients will be reviewed centrally to confirm a diagnosis of classical HL. Immunohistochemistry (to include CD20, CD30, CD15) will be performed. EBV status of the RS cells will be determined using LMP1 protein expression. The presence or absence of cKit and Caspase III expression will also be assessed.

Subsidiary Objectives

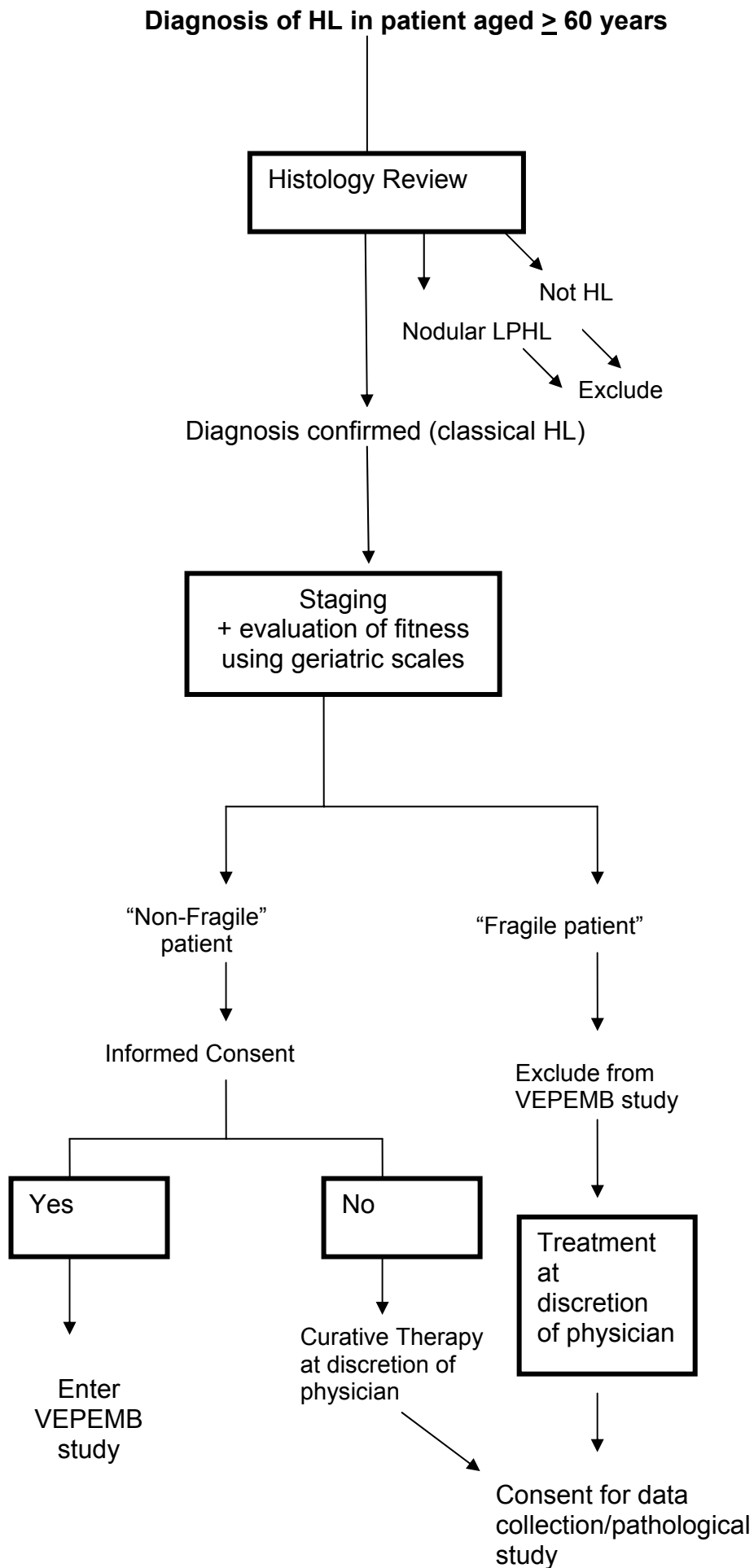
Serum (10 mls taken prior to treatment) will be stored at – 70°C in aliquots in Newcastle. These will be used to estimate LDH and B₂ Microglobulin if this has not been done at the original hospital. Levels of sCD30 will also be measured.

Applicability of Prognostic Factors

Various prognostic indices have been formulated over the last few years (SNLG, Hasenclever) but none have been formulated or validated on older patients. The Hasenclever score will be applied to all study patients at diagnosis to see if this is valid in this age group. The possibility of a novel index for older patients from information garnered in this study will also be explored.

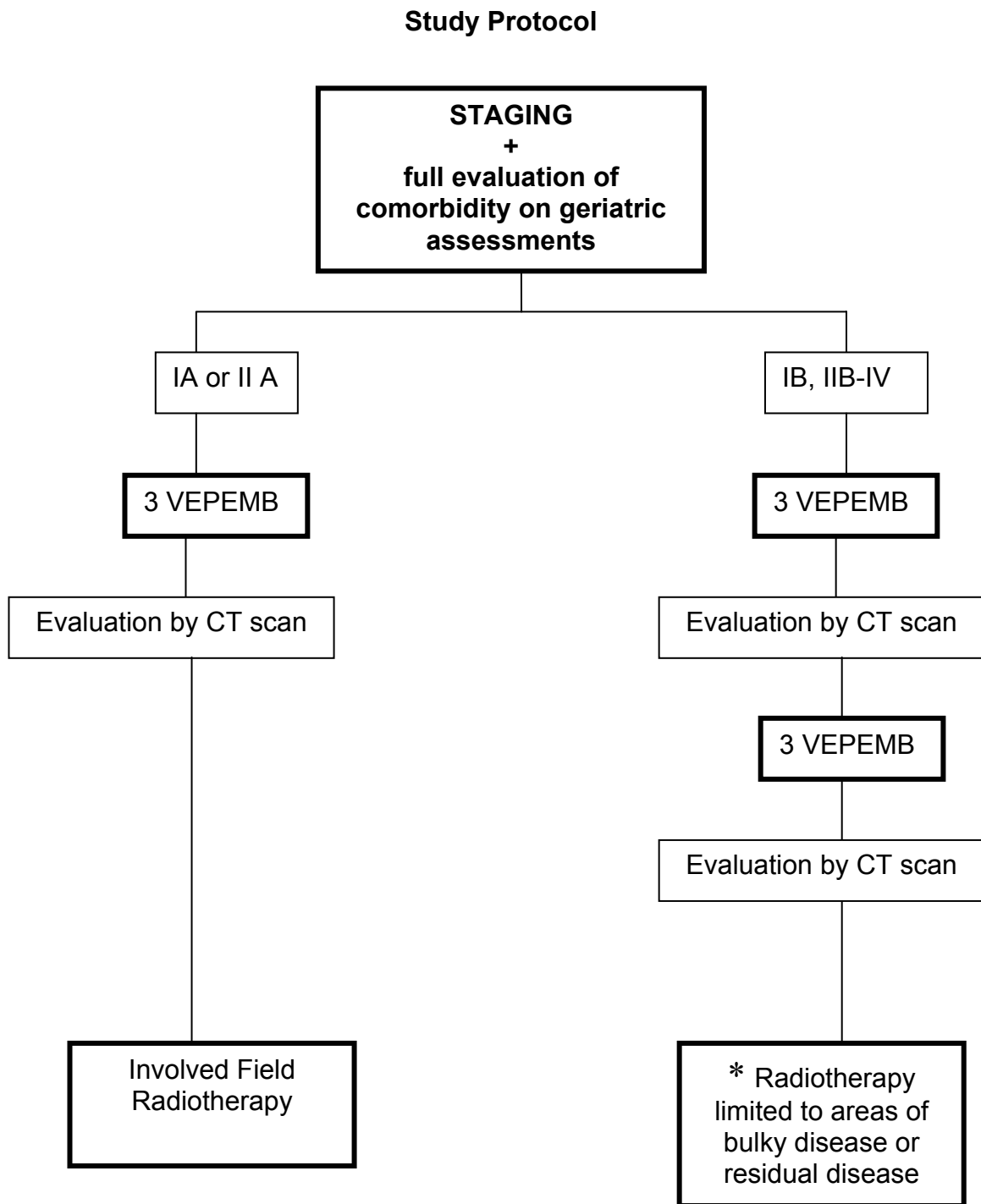
Study Summary

Figure 1



Study Summary

Figure 2



* Bulk disease = masses > 10cm at diagnosis

4. Eligibility

Inclusion Criteria

- Histologically confirmed classical Hodgkin Lymphoma (HL).
- No previous treatment for HL.
- Age > 60.
- “Non fragile” patient (see Appendix 1) i.e. patient’s mental and physical status must be sufficient to withstand the treatment described.
- No concomitant neoplasia or known HIV infection.
- Written informed consent.

Exclusion Criteria

- Nodular lymphocyte predominance Hodgkin Lymphoma (NLPHL)
- Age <60.
- Patient previously treated for HL.
- Known HIV infection or concomitant neoplasia.
- “Fragile patient” (see Appendix 1) or significant abnormality of another system (pulmonary, cardiac, renal, and hepatic) which is a contraindication to full dose chemotherapy.
- Unable to give informed consent.

5. Pre Registration Investigations

- Diagnosis of classical HL by local pathologist (all histology to be sent for central review).
- Evaluation of presence or absence of “*geriatric syndrome*” (Appendix 2).
- Evaluation of performance status (Appendix 3), comorbidity (Appendix 4), activities of daily living score (ADL, Appendix 5) and instrumental activities of daily living score (IADL, Appendix 6).
- Clinical assessment of adenopathy and systemic “B” symptoms.
- Chest X-ray.
- CT scan thorax, abdomen and pelvis.
- Bone marrow biopsy if B symptoms present or abnormal FBC.
- FBC, ESR, biochemistry to include B₂ microglobulin, LFT’s, urea and electrolytes, LDH, albumin.
- HIV and hepatitis C status if clinically indicated.
- Calculation of Hasenclever index (Appendix 7).

Evaluation of cardiac (ECHO) and pulmonary status (spirometry) if clinically indicated.

6. Registration and Randomisation

Centres must send a copy of their LREC's approval letter to the Newcastle Study office before registering their first patient.

Send the registration form (Appendix 8) by FAX to:

0191 222 5524 - Monday to Friday 9.00 to 5.00 pm

In case of problems contact:

Mrs J Wilkinson	0191 222 7632
Dr P Taylor	0191 282 5249
Prof S Proctor	0191 282 4262

Note: Once a patient has been registered that patient remains in the study regardless of treatment given, and full documentation and follow up will be required.

7. Plan of Treatment

After therapy allocation the patient will be treated according to their clinical stage.

Early Stage

- Patients with stage 1A and 2A disease are treated with 3xVEPEMB (details of chemotherapy see below) plus involved field radiotherapy.

The Involved Field Radiotherapy will be as follows:-

- Timing – radiotherapy will be planned to commence a minimum of 4 weeks after completion of chemotherapy.
- Equipment – megavoltage photons.
- Volume – all initially involved nodal sites to be included in the planning target volume with minimum margins of 5cms craniocaudally (in direction of lymphatic drainage) and 2cms laterally. The lateral margins to be planned on the post chemotherapy imaging to avoid unnecessary irradiation of normal tissues such as lung.
- Technique – parallel opposed anterior and posterior fields will be used with individualised shielding blocks or MLC's
- Dose – 30Gy/15-20f to consolidate CR. 35Gy/20f for persistent disease.

Advanced Stage

- Patient with stage 1B, 2B to 4 disease are treated with 6 cycles of chemotherapy (VEPEMB).
- For dose modification see below.
- Details of supportive therapy will be found in a separate section.

Radiotherapy will only be given to sites of initial bulk disease (> 10 cm) and to areas of residual disease as follows:

- Timing – radiotherapy will be planned to commence a minimum of 4 weeks after completion of chemotherapy.
- Equipment – megavoltage photons.
- Volume – planning target volume will include
 1. Initial sites of bulk disease including all nodal sites > 10cm at presentation and the mediastinum if mediastinum to thoracic ratio > 1/3 at T5/T6 junction at presentation.
 2. Sites of persistent disease.
Minimum margins will be 5cm craniocaudally (in direction of lymphatic drainage) and 2cms laterally. The lateral margins will be based on post chemotherapy imaging to spare normal tissues.
- Technique – parallel opposed anterior and posterior fields with individualised shielding blocks or MLC's
- Dose – 30Gy/15-20f to consolidate CR. 35Gy/20f for persistent disease.

Chemotherapy Schedule

VEPEMB													
	Dose Mg/m²	Route	Day 1	Day 2	Day 3	Day 4	Day 5		Day 15	Day 16	Day 17	Day 18	Day 19
Vinblastine	6	lv	*					—					
Cyclophosphamide	500	IV	*					—					
Procarbazine	100	po	*	*	*	*	*	—					
Prednisolone	30	po	*	*	*	*	*	—					
Etoposide	60	po						—	*	*	*	*	*
Mitoxantrone	6	lv						—	*				
Bleomycin	10	lv						—	*				
Cycle repeated every 28 days													

V – Vinblastine

E – (Endoxana), Cyclophosphamide

P – Procarbazine/Prednisolone

E – Etoposide

M – Mitoxantrone

B - Bleomycin

Chemotherapy Schedule Modifications

Dose decisions to be made in Day 1 and 15 of each course.

The aim is to give full doses rather than dose reductions.

- | | | | | |
|----|-------------------|---------------------------|---|---|
| 1. | Granulocyte count | $> 2.0 \times 10^9/l$ |) | full dose |
| | Platelet count | $> 100 \times 10^9/l$ |) | |
| 2. | Granulocyte count | $1.0 - 2.0 \times 10^9/l$ |) | Delay 1 week |
| | Platelet | $50-100 \times 10^9/l$ |) | Give GCSF support |
| 3. | Granulocyte count | $< 1.0 \times 10^9/l$ |) | delay until granulocytes $> 2.0 \times 10^9/l$. Give GCSF support to |
| | Platelet | $< 50\% 10^9/l$ |) | minimise delay. |

In patients where granulocyte count remains chronically reduced ($< 2.0 \times 10^9/l$) in spite of growth factors support. Proceed with 50% reduction of all drugs except prednisolone and bleomycin.

Pilot data indicates that GCSF support is necessary to maintain dose intensity, but this is variable in the number of days per course in individual patients. It increases as the patient proceeds through the protocol. If GCSF is to be used, utilise between days 7 to 15 and days 21 to 28 of the monthly schedule.

8. Other Treatment Issues

Supportive Therapy

a. Anti infective Prophylaxis

Pneumocystis carinii prophylaxis is recommended in all patients for the duration of chemotherapy. Cotrimoxazole oral 960 mg Monday, Wednesday and Friday except in patients on oral anticoagulants where alternatives should be used.

If patients have a neutrophil count of $<0.5 \times 10^9/l$ prophylactic antibiotics (Ciprofloxacin) and antifungals (Fluconazole) are recommended.

b. In episodes of neutropaenic sepsis GCSF therapy is recommended. Use of GCSF may be necessary to maintain dose intensity (see previous section).

Adverse Event

a. Adverse Event Reporting

Any new diagnosis, any reason for referral to a consultant or admission to hospital, any unexpected deterioration in a concurrent illness, any suspected drug reaction, or any complaint which is considered of sufficient importance to enter the subject's notes will be reported in the appropriate section of the CRF.

For each adverse event, the Investigator will report in the case report form the following information:

- type
- date of onset
- severity
- outcome
- drug relationship
- the most probably cause of the event in the Investigator's opinion
- if medical or surgical treatment was required.

In the case of serious or unexpected adverse events, the study coordinator will be contacted by the treating physician laying out details of such an event. If in the opinion of the treating physician such an adverse event can be designated to any particular part of the protocol treatment such information would be passed to the drug companies concerned.

He must also provide a completed adverse event report within 3 days for "fatal" and within 10 days for "serious" events. Whenever possible, should any fatality occur within 30 days after the end of the study, it will also be reported.

9. Evaluation of Response

These will occur:

- After the first 3 courses of chemotherapy.
- At the end of chemotherapy (if receiving 6 courses).
- After radiotherapy if this is given after chemotherapy.

Evaluation

- Measurement of any clinical residual adenopathy.
- Assessment of presence or absence of B symptoms.
- Full biochemical profile and FBC, ESR.
- CT scan of chest, abdomen and pelvis.
- Bone Marrow aspirate and trephine if initially positive (at end of treatment).
- Optional assessment by PET or gallium scan if residual disease is present.

Definition of Response

Complete Remission (CR):	total disappearance of all evidence of disease.
CR (U):	persistence of a residual mass of uncertain significance.
Partial Remission (PR):	reduction of 50% or more in size of all lesions present at diagnosis and no new lesions seen.
No Remission (NR):	less than 50% of reduction of measurable lesions.
Progressive Disease (PD):	Increase in size of existing lesions or presence of new lesions.

10. Follow up

Following the end of treatment, patients will be seen at monthly intervals for 3 months, then 3 monthly for 6 months, thereafter follow up will be annually (if possible to coincide with the anniversary of diagnosis).

Investigations at follow-up

- I. Clinical assessment of presence/absence of adenopathy.
- II) Assessment of presence or absence of B symptoms.
- III) Follow-up CT scan at discretion of clinician (mandatory at 6 months post treatment if residual mass is present at the end of treatment scan).

11. Data Collection/form completion

All data will be collected and evaluated in the Study Office at Newcastle. For each centre submitting patients there will be a named investigator who will be responsible for ensuring prompt return of data and for ensuring the central review of histology.

- The completed therapy allocation form (Appendix 8) should be faxed once the patient has consented to the study.
- The staging and evaluation of “geriatric fragility” scores (staging Appendix 2), co-morbidity (Appendix 4), ADL score (Appendix 5), IADL score (Appendix 6), should be performed prior to treatment allocation or shortly afterwards.
- Patient clinical record form (Appendix 9(a)) should be completed and returned as soon as possible after the end of treatment or when the patient comes off study.
- Follow up (Appendix 9(b) and (c)) should be performed annually, on or close to the anniversary of diagnosis.
- Serious adverse events should be reported within two working days to the central Study Office.

Address for the co-ordinating centre:

Study Office for Hodgkin’s Disease in the Elderly Study Group
Haematological Sciences
School of Clinical & Laboratory Sciences
Leech Building
Medical School
Framlington Place
Newcastle upon Tyne
NE2 4HH

Tel: 0191 222 7791

Fax: 0191 222 5524

E-mail: Clinical issues: Professor S J Proctor [S.J. Proctor@ncl.ac.uk](mailto:S.J.Proctor@ncl.ac.uk)
Dr P Taylor dept.haem@ncl.ac.uk

Data management issues: jennifer.wilkinson@ncl.ac.uk

12. Endpoints

The primary endpoints will be progression-free survival, with clinical progression and death as the events. On suspicion of progression (e.g. new or enlarging masses, development of 'B' symptoms) patients should be re-evaluated according to normal procedures to confirm relapse. Histological confirmation of relapse is recommended but not mandatory.

Survival time, including death from any cause, will also be investigated. For both endpoints, the event-free times will be dated from the date of histological diagnosis.

Subsidiary Endpoints

Analysis will be done to assess potential prognostic factors (EBV status, "Fragility" assessment, Hasenclever index, sCD30) which might be relevant in this age group.

Quality of Life Assessments (see Appendix 11)

These will be for study patients only and will be performed at diagnosis, end of treatment, and two years and five years post diagnosis.

13. Statistical considerations

The study has been powered with respect to the principal clinical hypotheses, to enable reasonably accurate estimation of the progression-free survival rate amongst those patients undergoing protocol chemotherapy.

Sample Size and Power

150 patients are required for completion of this study. It is anticipated that the complete remission rate will be of the order of 2/3 (66%). This is based on an expectation that around 40-50% of patients will be of stage I or II, with a high CR rate close to 90%. The remaining patients of stage III or IV are likely to achieve a CR rate of around 50%. With 150 patients recruited, the likely standard error of the CR rate will be approximately 3.9%, and will be less than 4.1%, whatever the eventual CR rate. If 100 patients enter CR, then the percentage with an enduring CR at 1 year will be estimated with a standard error of 5% or less. If the estimated rate of CR proves inaccurate, then with 80 entering CR, the maximum standard error of the percentage still in CR at one year will be 5.6% or less, and with 60 in CR, this maximum standard error will increase to 6.5%.

Methods

As this is a Phase II clinical study, the patients are from a single group, and will be analysed using descriptive statistics. The principal outcomes are the complete remission rate, and the probability of remaining disease free at one year. 95% confidence intervals will be reported for each of these outcomes. The main focus of the analysis will be on the population of patients who commence treatment. A subsidiary analysis will be based on the patients who achieve complete remission, and the proportion remaining in complete remission over time will be shown using the Kaplan-Meier method.

The survival of the total population will also be presented using the Kaplan-Meier method. An exploratory analysis will examine patient factors affecting survival, using a Cox proportional hazards model. Factors affecting the achievement of complete remission will be investigated using linear logistic regression models.

Registered patients not on VEPEMB Study Protocol will be presented using descriptive statistics with Kaplan-Meier curves used to summarise the survival experience. The data will be analysed for the influence of potential prognostic factors on survival and examined with the study patients to see if the same prognostic factors apply.

Quality of Life

The quality of life assessments will be analysed using repeated measures analysis of covariance, with baseline levels, age and sex as covariates. Attention will focus on the overall treatment effect and whether there are significant treatment by time interactions.

Anticipated Accrual Rate

Data from the Northern Region Population Study indicates that approximately 250 cases of Hodgkin's disease \geq 60 years occurs in the UK annually. 50% might be considered for curative treatment. A realistic accrual would be of 50 cases per annum giving a recruitment period of 36 months. Additional centres within main land Europe might shorten this accrual period.

Data Collection

The aim is to collect basic data on the patients with Hodgkin's lymphoma \geq 60 years utilising the enclosed forms (all patients) and for those who are on the VEPEMB study on the enclosed CRF forms. The basic data will be collected using paper or electronic submission. The details of the electronic programme will comply with guidelines of the Computing Department, University of Newcastle upon Tyne, fulfil the criteria required under the Caldicott guidelines of the Newcastle Hospitals Trust and comply with the Data Protection Act.

All major lymphoma organisations within the UK have agreed to participate under the auspices of the NCRN.

Data Monitoring Committee

Chairman Professor Barry Hancock (Sheffield). Members to be appointed.

14. Ethical Considerations

This study will have been approved by the Multicentre Research Ethics Committee (MREC) and must also be approved by the Local Research Ethics Committee (LREC) at each centre before patients are entered. A copy of a centre's LREC approval must be lodged with the study office in Newcastle before entry of patients can commence at that centre. Centres are required to register with the Study Office before recruitment starts.

The right of a patient to refuse to participate in the study without giving reasons must be respected. After the patient has entered the study, the clinician is free to give alternative treatment to that specified in the protocol at any stage if he/she feels it to be in the patients best interest. The patient may withdraw at any time from the study without giving reasons or prejudicing future treatment. Once they have been given consent, all patients who come off study treatment for whatever reason will still remain in the study for follow up and data analysis.

This study will be conducted according to the Medical Research Council's "Guidelines for Good Clinical Practice in Clinical Trials".

15. Publication

The data from the participating centres will be analysed together and published as soon as possible. All participating clinicians will be identified in addition to the Chief and Principle Investigators and Statistician. Individual clinicians must not publish either data concerning their patients which are directly relevant to the questions posed by the study, or interim analyses of the collective data, until such time as the main results of the study have been published.

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Definition of a “Frail” Patient

“NON FRAIL” (eligible for the VEPEMB study)

Positive for all the following conditions:

1. Less than 3 comorbidity of grade 3 and absence of any comorbidity grade 4.
 2. ADL score not lower than 6.
 3. Any IADL score.
 4. Absence of “geriatric syndrome”.
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“FRAIL” (not eligible for the VEPEMB study)

1. Three or more comorbidities of grade 3.
2. One or more comorbidities of grade 4.
3. ADL score less than 6.
4. Presence of “geriatric syndrome”.

Ref: Ferrucci L, Guralnik JM, Cavazzina C, et al. The frailty syndrome: a critical issue in geriatric oncology. *Critical Reviews in Oncology/Haematology* 2003;46:127–137.

Definition of “geriatric syndrome”

“Geriatric syndrome” is the presence of one or more of the following:

	No	Yes
Dementia	<input type="checkbox"/>	<input type="checkbox"/>
Confused State	<input type="checkbox"/>	<input type="checkbox"/>
Depression	<input type="checkbox"/>	<input type="checkbox"/>
Urinary and/or faecal incontinence	<input type="checkbox"/>	<input type="checkbox"/>
Severe Osteoporosis	<input type="checkbox"/>	<input type="checkbox"/>
Falls	<input type="checkbox"/>	<input type="checkbox"/>
Neglect and abuse	<input type="checkbox"/>	<input type="checkbox"/>

Definitions

Dementia	Clinical diagnosis
Confused state	During a urinary or pulmonary infection or due to a drug which normally does not cause this.
Depression	Clinical diagnosis
Incontinence (faecal or urinary)	Unless due to immobility eg. secondary to arthritis.
Osteoporosis	If associated with fractures.
Falls	3 or more per month.
Neglect and Abuse	

Evaluation of Performance Status

0	Asymptomatic normal activity.
1	Minor symptoms but near normal activity.
2	Moderate symptoms, limitation of function.
3	Severe limitation of function.
4	Bedridden.
5	Dead.

COMORBIDITY SCALE

	SCORE				
HEART (heart only)	1	2	3	4	5
HYPERTENSION (hypertension severity is considered)	1	2	3	4	5
VASCULAR (both venous and artery districts)	1	2	3	4	5
DIABETES	1	2	3	4	5
RESPIRATORY	1	2	3	4	5
GASTROINTESTINAL	1	2	3	4	5
LIVER	1	2	3	4	5
KIDNEY	1	2	3	4	5
OTHER GENITO-URINARY	1	2	3	4	5
BONE and MUSCLE	1	2	3	4	5
NERVOUS SYSTEM (central and peripheral, dementia is excluded)	1	2	3	4	5
EYES and ENT (eyes, ears, nose, larynx)	1	2	3	4	5
ENDOCRINE SYSTEM and METABOLISM (diabetes excluded)	1	2	3	4	5

Legend

1. **No disability.**
2. **Low disability** (it does not interfere with normal activities; treatment is optional; very good prognosis).
3. **Mild disability** (it interferes with normal activities; treatment is needed, good prognosis).
4. **Severe disability** (disabling, urgent treatment is needed; poor prognosis).
5. **Very severe disability** (it can be fatal; emergency treatment is needed; danger list).

FRAIL PATIENT: three or more items of grade 3 or one or more of grade 4.

ADL Score**Activities of Daily Living Score**

Centre: _____

Patients Name: _____ Date ___/___/___/

.....

Function	Description	Score	
		YES 1	NO 0
Bathing	Can get in and out of bath or shower unsupervised and unaided	<input type="checkbox"/>	<input type="checkbox"/>
Dressing	Needs help when dressing (including zips, laces, buttons) but can do about half unaided.	<input type="checkbox"/>	<input type="checkbox"/>
Toilet Use	Needs some help with dressing/undressing or wiping but can manage otherwise	<input type="checkbox"/>	<input type="checkbox"/>
Continence	In control of bladder and bowels (allowed occasional accidents)	<input type="checkbox"/>	<input type="checkbox"/>
Balance	Able to sit unaided (allowed help to get upright)	<input type="checkbox"/>	<input type="checkbox"/>
Feeding	Able to feed without assistance (help with cutting meat, spreading butter etc allowed)	<input type="checkbox"/>	<input type="checkbox"/>

Maximum score 6

Instrumental Activities of Daily Living

Centre: _____

Patients Name: _____ Date ___/___/___/

		POINTS
A	The ability of use the phone	
	<ul style="list-style-type: none"> • Operates telephone on own initiative. • Dials a few well known numbers. • Answers telephone but does not dial. • Does not use telephone at all. 	1 1 1 0
B	Shopping	
	<ul style="list-style-type: none"> • Takes care of all shopping needs independently • Shops independently for small purchases. • Needs to be accompanied on any shopping trip. • Completely unable to shop.. 	1 0 0 0
C	Food Preparation	
	<ul style="list-style-type: none"> • Plans, prepares and serves adequate meals independently • Prepares adequate meals which are supplied with ingredients. • Heats, serves and prepares meals but does not maintain adequate diet. • Needs to have meals prepared and served. 	1 0 0 0
D	Housekeeping	
	<ul style="list-style-type: none"> • Maintain house alone or with an occasional activity. • Performs light daily tasks such as dishwashing or bed making. • Performs light daily tasks but cannot maintain acceptable level of cleanliness. • Needs help with all house maintenance tasks. • Does not participate in any housekeeping tasks. 	1 1 1 1 0
E	Laundry	
	<ul style="list-style-type: none"> • Does personal laundry completely. • Does small items by herself/himself. • All laundry must be done by others. 	1 1 0
F	Mode of Transportation	
	<ul style="list-style-type: none"> • Travels independently. • Arranges own travel by taxi but does not use other modes of transportation. • Travels on public transportation when accompanied by others. • Travels limited to full assistance by others. 	1 1 1 0
G	Responsibility for medications.	
	<ul style="list-style-type: none"> • Is able to take medications in correct dosages at a correct time. • Takes medication if they are prepared in advance at correct dosages. • Is not capable of dispensing own medications. 	1 0 0
H	Ability to Handle Finance	
	<ul style="list-style-type: none"> • Manages financial matters independently. • Manages day to day purchases but needs help with banking major purchases etc. • Incapable of handling money. 	1 0 0

Maximum total possible = 8.

Calculation of the Hasenclever Score

Score 1 point for each factor present.

FACTORS

Age \geq 45 years (always present)

Male Sex

Stage 4

Serum albumin $<$ 40g/l

Haemoglobin $<$ 10.5 g/dl

WCC $>$ $15 \times 10^9/l$

Lymphocyte count $<$ $0.6 \times 10^9/l$ or $<$ 8% of total WCC

SCORE

$<$ 3, low risk

3-4 intermediate risk

\geq 5 high risk

Hodgkin's in the Elderly Study

Therapy Allocation Form

Fax to: Haematological Sciences, School of Clinical & Laboratory Sciences, Leech Building, Medical School, Framlington Place, Newcastle upon Tyne, NE2 4HH.

Number: 0191 222 5524

Hospital: _____

Consultant: _____

Patient Data

Patient Name: _____				
Date of Birth: /__ / __ / __ /	Sex <input type="checkbox"/> M <input type="checkbox"/> F			
Date of Diagnosis: /__ / __ / __ /				
Stage	<input type="checkbox"/> I	<input type="checkbox"/> II	<input type="checkbox"/> III	<input type="checkbox"/> IV
B symptoms	<input type="checkbox"/> A	<input type="checkbox"/> B		
Histology	<input type="checkbox"/> NS	<input type="checkbox"/> MC	<input type="checkbox"/> LD	
Comorbidity	<input type="checkbox"/> Yes			
	<input type="checkbox"/> No (see Appendix 4)			
ADL score (see Appendix 5): _____				
IADL score (see Appendix 6): _____				
Performance status (see Appendix 3): _____				

Allocation of treatment:

Patient Name: _____	
Date of randomisation: /__ / __ / __ /	Study number: _____
Assigned treatment:	<input type="checkbox"/> VEPEMB <input type="checkbox"/> Other therapy, specify

Study of Hodgkin's Disease In the Elderly/Lymphoma Database
SHIELD STUDY

A. PILOT DEMOGRAPHICS

Unique patient number : Patient Age Year & month of birth ----/---
 Hospital or Study Group:
 Male/Female

B. CLINICAL AND RADIOLOGICAL DATA

1. Patient performance data	Total Score	Not Known	Not Done
(a) ECOG fitness rating	<input type="text"/>	<input type="text"/>	<input type="text"/>
(b) Activity of daily living score	<input type="text"/>	<input type="text"/>	<input type="text"/>
(c) Instrument of activity score	<input type="text"/>	<input type="text"/>	<input type="text"/>
(d) <u>Co-morbidity rating scale : ACE-27</u>			
Overall co-morbidity (circle)	0 1 2 3	<input type="text"/>	<input type="text"/>

2. Clinical Staging

	Done	Not done
CT Scan	<input type="text"/>	<input type="text"/>
MRI Scan	<input type="text"/>	<input type="text"/>
Chest Xray	<input type="text"/>	<input type="text"/>
Abdominal ultrasound	<input type="text"/>	<input type="text"/>

Clinical Stage: (Appendix IV)

Stage IA	<input type="text"/>	Stage IB	<input type="text"/>	Not Staged	<input type="text"/>
Stage IIA	<input type="text"/>	Stage IIB	<input type="text"/>		
Stage IIIA	<input type="text"/>	Stage IIIB	<input type="text"/>		
Stage IVA	<input type="text"/>	Stage IVB	<input type="text"/>		

No. of nodal sites (specify)

If Stage IV, specify each extra nodal site, e.g. marrow, liver etc.

Bulk disease: **None**

If yes, specify

>33% CT ratio	<input type="text"/>
> 5cms any other site	<input type="text"/>
> 10cms any other site	<input type="text"/>

C. PRE-TREATMENT DIAGNOSTIC INVESTIGATIONS (I)

	Specify	Not Known	Not Done
Haemoglobin(g/l)	<input type="checkbox"/>	<input type="checkbox"/>
ESR(mm/hr)	<input type="checkbox"/>	<input type="checkbox"/>
Total WBC(x 10 ⁹ /l)	<input type="checkbox"/>	<input type="checkbox"/>
Absolute lymphocyte count (x 10 ⁹ /l)	<input type="checkbox"/>	<input type="checkbox"/>
Bone Marrow	Positive	Negative	Not Known
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

PRE-TREATMENT DIAGNOSTIC INVESTIGATIONS (II)

	Normal	Not Normal	Specify Level	Not Known	Not Done
CRP	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Albumin g/dl	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
B ₂ Microglobulin	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Soluble CD 30	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Serum IL10	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Serum Stored	Yes <input type="checkbox"/>	No <input type="checkbox"/>		<input type="checkbox"/>	
Multiple aliquots	Yes <input type="checkbox"/>	No <input type="checkbox"/>		<input type="checkbox"/>	

D. PROGNOSTIC CATEGORY

1. Hasenclever/Diehl Int. Index
 Number of risk factors: <3 3-4 ≥ 5

2. Local index or risk category for Centre/Organisation
 Specify index and score.....

E. HISTOLOGY

Date of primary biopsy..... Place Performed..... Number.....

Sent for review: Yes No Date of review

Place of review (specify)..... Confirms diagnosis: Yes No

Histology review number Confirms sub-type: Yes No

F. HODGKIN LYMPHOMA CLASSIFICATION (WHO)

Nodular lymphocyte predominant

Classical Hodgkin's disease:

Nodular sclerosis	<input type="checkbox"/>	Mixed cellularity	<input type="checkbox"/>
Lymphocyte depleted	<input type="checkbox"/>	Lymphocyte rich (classical)	<input type="checkbox"/>
Unclassified	<input type="checkbox"/>		

G. ANTIGEN PROFILE AT DIAGNOSIS

Known	Weak			Not Done	Not
	Positive	Positive	Negative		
CD30	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CD 15	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Epithelial membrane antigen (EMA)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CD 20	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
EBV (LMP-I/EBER)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
CD 3	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

H. PRIMARY THERAPY INTENTIONS

To cure Palliative Supportive

	Yes	No
(1) Chemotherapy alone	<input type="checkbox"/>	<input type="checkbox"/>
Is chemotherapy designated by study	<input type="checkbox"/>	<input type="checkbox"/>
If yes, SHIELD study (VEPEMB)	<input type="checkbox"/>	Planned number of cycles
If no, alternative planned therapy. Specify:		

	Yes	No	
(2) Radiotherapy	<input type="checkbox"/>	<input type="checkbox"/>	Date started
Specify field			Specify fraction ...
Specify dose.....			

	Yes	No
(3) Combined Therapy	<input type="checkbox"/>	<input type="checkbox"/>
If yes, specify order, e.g. (1)+(2),(2)+(1)		

(N.B. This is not a case report form for the study but a basic data collection form for all patients).

Study of Hodgkin's disease in the Elderly/Lymphoma Database
SHIELD STUDY

FIRST ANNUAL FOLLOW-UP FORM

Dates covered by this form (month/year).....→ (month/year).....

A. Study Identifier

SHIELD patient No:Study Centre NoDate last seen

Status at date last seen: Alive Dead Untraceable

Evidence of secondary malignancy: Yes No Not known

B. Treatment for lymphoma during these 12 months

Yes No

Reason if treatment not given

If, Yes: Date started

Type of primary therapy:

1. Radiotherapy 2. Chemotherapy 3. Surgery 4. Other

If surgery, curative? Yes No

What type of surgery.....

If combined modality, indicate sequence (i.e. 1+2)

Radiotherapy:

Site One

Yes No Date started No of fractions

Area irradiated Total dose Gy

Site Two

Yes No Date started No of fractions

Area irradiated Total dose Gy

Chemotherapy:

Yes No Date started

Specify:

Number of courses planned: Number of courses given:

On trial/study:

Yes Specify

No Specify reason

	<u>Yes</u>	<u>No</u>
C. Growth factor used during chemotherapy	<input type="checkbox"/>	<input type="checkbox"/>
If Yes , prophylactic	<input type="checkbox"/>	<input type="checkbox"/>
If Yes , GCSF <input type="checkbox"/> Erythropoietin	<input type="checkbox"/> Both	<input type="checkbox"/>
Days of GCSF per cycle of treatment: Specify		
Chemotherapy dose modification?	<input type="checkbox"/>	<input type="checkbox"/>
In-patient hospital episodes	<input type="checkbox"/>	<input type="checkbox"/>
If Yes , number of episodes <input type="text"/>		
Specify (number of inpatient days) :		

D. State of lymphoma after primary therapy

	Yes	Date
CR, no radiological abnormality	<input type="checkbox"/>
CR(u) unconfirmed/unproven/uncertain	<input type="checkbox"/>
Part-remission achieved	<input type="checkbox"/>
No remission/static	<input type="checkbox"/>
Relapse/progression	<input type="checkbox"/>
Biopsy proven?	<input type="checkbox"/>	No <input type="checkbox"/>

E. Treatment subsequent to primary therapy

	Yes	No
Treatment subsequent to primary therapy started in the above 12 months?	<input type="checkbox"/>	<input type="checkbox"/>
If yes, date started		

Type of subsequent therapy

Radiotherapy Chemotherapy Surgery BMT/PBSC Other

If surgery or other, specify

If combined modality, indicate sequence

Chemotherapy

Drug Schedule Specify.....

BMT conditioning regimen (if applicable)

On trial/study

Yes Specify

No Why

Radiotherapy:

Yes No

Date started

Number of fractions

Area irradiated

Total dose given in (Gy)

F. Death

Date of death

Principle cause of death

:

Other relevant details

.....

Comments

.....

Study of Hodgkin's disease in the Elderly/Lymphoma Database
SHIELD STUDY

ANNUAL FOLLOW-UP FORM : SECOND AND SUBSEQUENT YEARS

Dates covered by this form (month/year).....→ (month/year).....

A. Study Identifier

SHIELD patient number: Study Centre No

B. Status of Patient

Untraceable:

Status of patient at last annual follow-up date: Alive Dead

Date last seen: (dd/mm/yyyy) (-- / -- / ----)

Disease state at last consultation: CR PR Relapsed

Date of relapse / progression (dd/mm/yyyy) (-- / -- / ----)

Biopsy proven: Yes No

C. Treatment begun within last year

None

If Yes, date: (dd/mm/yyyy) (-- / -- / ----)

Chemotherapy Specify

Radiotherapy Specify

D. Evidence of other malignancy

Yes No Specify

E. Death

Date of death: (dd/mm/yyyy) (-- / -- / ----)

Cause of death: Progressive Hodgkin's disease Other

Specify

Treatment related? Yes No

F. Comments (e.g. Late side-effects of treatment; patient toleration of chemotherapy; transfer of care elsewhere)

.....

Common Toxicity Criteria

Explanatory Notes

1. Toxicities are grouped into the following categories based on body system:

Allergy	Hepatic
Blood/bone marrow	Infection
Cancer-related symptoms	Metabolic
Cardiovascular	Neurologic
Coagulation	Ocular
Dentition (teeth)	Osseous (bone)
Endocrine	Other
Flu-like symptoms	Pulmonary
Gastrointestinal	Skin
Genitourinary	Weight

2. Protocols requiring detailed hypersensitivity reaction reporting will include a Hypersensitivity Reaction Module.
3. Categories are listed alphabetically, with toxicity variables (eg: dysrhythmia, nausea, dizziness) listed alphabetically within each category.
4. Toxicity codes are composed of a 2-character “prefix” based on toxicity category, and a 3-character “description” based on variable name. For example:(cardiovascular) dysrhythmia = CD DYS, (gastrointestinal) nausea = GI NAU, (neurologic) dizziness = NE DIZ
5. Some conventions: = hyper (or high) (eg: CD HBP = hypertension)
L = hypo (or low) (eg: MT LCA = hypocalcaemia)
6. Codes are usually derived from the first 3 letters of the toxicity variable (eg: nausea = GI NAU). Exceptions to this rule have been made in the following cases:
 - where the first 3 letters are not particularly helpful or descriptive (eg: mouth dryness has been coded GI DRY instead of GI MOU)
 - where the first 3 letters are potentially confusing (eg: flushing, facial has been coded SK FAC instead of SK FLU)
 - where a “common” 3 letter abbreviation already exists (eg: haemoglobin has been coded BL HGB instead of BL HEM)
7. For toxicities which do not have an existing code, but do fit into an existing toxicity category, use “other” variable in the appropriate toxicity category (eg: code pathologic fracture OSSEOUS OTHER (OS OTH). For toxicities which do

not have existing codes, and do NOT fit into existing categories, code OTHER OTHER (OT OTH).

8. Please note that ONLY the codes listed in the criteria may be used. Data managers should not “create” new toxicity codes. If a new toxicity is identified which doesn’t have an existing code or doesn’t fit an existing category, use OTHER and OTHER OTHER variables as outlined above. If you’re unsure how to code a particular toxicity, please record toxicity type only on the form.

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
GRADE	0	1	2	3	4	
ALLERGY						
AL LER Allergy	None	Transient rash, fever <38°C, 100.4°F	Urticaria, fever = 38°C, 100.4°F, mild bronchospasm	Serum sickness, bronchospasm, req parenteral mode	Anaphylaxis	
Fever felt to be caused by <u>drug allergy</u> should be coded as ALLERGY (AL LER). <u>Non-allergic</u> drug fever (eg: as from biologics) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to <u>infection</u> , code INFECTION only (IN FEC or IN NEU). NB: Protocols requiring detailed reporting of hypersensitivity reactions, will include a Hypersensitivity Reaction module.						
AL OTH Other*	None	Mild	Moderate	Severe	life threatening	
BLOOD/BONE MARROW (SI UNITS)						
BL WBC White Blood Count (WBC)	≥4.0 10 ⁹ /L	3.0-3.9	2.0-2.9	1.0-1.9	<1.0	
BL PLT Platelets	WNL 10 ⁹ /L	75.0 normal	50.0-74.9	25.0-49.9	<25.0	
BL HGB Hemoglobin (Hgb)	WNL g/L	100 normal	80-99	65-79	<65	
BL GRA Granulocytes (ie. neuts + bands)	≥2.0 10 ⁹ /L	1.5-1.9	1.0-1.4	0.5-0.9	<0.5	
BL LYM Lymphocytes	≥2.0 10 ⁹ /L	1.5-1.9	1.0-1.4	0.5-0.9	<0.5	
BL HEM Hemorrhage resulting from thrombocytopenia (clinical)	None	Mild, no transfusion (inc bruise/hematoma, petechiae)	Gross, 1 - 2 units transfusion per episode	Gross, 3 - 4 units transfusion per episode	Massive, >4 units transfusion per episode	
BL OTH Other*	None	Mild	Moderate	Severe	Life threatening	
CANCER RELATED SYMPTOMS						
CA DEA Death from malignant disease within 30 days of treatment* (grd=5)	-		-	-	-	
CA PAI Cancer pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain	
CA SEC Second malignancy*	None	-	-	Present	-	
CA OTH Other*	None	Mild	Moderate	Severe	life threatening	
CARDIOVASCULAR						
CD ART Arterial* (non myocardial)	None	-	-	Transient events (eg: transient ischemic attack)	Permanent event (eg: cerebral vascular accident)	
CD VEN Venous*	None	Superficial (excl IV site reaction-code SK LTO)	Deep vein thrombosis not req anticoagulant therapy	Deep vein thrombosis req anticoagulant therapy	Pulmonary embolism	
CD DYS Dysrhythmias	None	Asymptomatic, transient, req no therapy	Recurrent or persistent, no therapy req	Req trt	Req monitoring, or hypotension, or ventricular tachycardia, or fibrillation	
CD EDE Oedema* (eg: peripheral oedema)	None	1+ or dependent in evening only	2+ or dependent throughout day	3+	4+, generalised anasarca	
CD FUN Function	None	Asymptomatic, decline of resting ejection fraction of ≥10% but < 20% of baseline value	Asymptomatic, decline of resting ejection fraction by >20% of baseline value	Mild CHF, responsive to therapy	Severe or refractory CHF	
CD HBP Hypertension	None or no change	Asymptomatic, transient increase by >20mm Hg (D) or to >150/100 if previously WNL. No trt req	Recurrent or persistent increase by >20mm Hg (D) or to >150/100 if previously WNL. No trt req	Req therapy	Hypertensive crisis	
CD LBP Hypotension	None or no change	Changes req no therapy (incl transient orthostatic hypotension)	Req fluid replacement or other therapy but not hospitalisation	Req therapy & hospitalisation: resolves within 48hrs of stopping agent	Req therapy & hospitalisation for >48hrs after stopping agent	

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA						REVISED: 94-DEC-21
GRADE		0	1	2	3	4
CD ISC	Ischemia (myocardial)	None	Non-specific T wave flattening	Asymptomatic, ST & T wave changes suggesting ischemia	Angina without evidence for infarction	Acute myocardial infarction
CD PAI	Pain (chest)*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
CD PER	Pericardial	None	Asymptomatic, effusion, no intervention req	Pericarditis (rub, chest pain, ECG changes)	symptomatic effusion; drainage req	Tamponade, drainage urgently req; or constrictive pericarditis req surgery
CD TAC	Sinus tachycardia*	None	Mild	Moderate	Severe	life threatening
CD OTH	Other*	None	Mild	Moderate	Severe	life threatening
COAGULATION						
CG FIB	Fibrinogen	WNL	0.99-0.75 x N	0.74-0.50 x N	0.49-0.25 x N	≤0.24 x N
CG PT	Prothrombin time	WNL	1.01-1.25 x N	1.26-1.50 x N	1.51-2.00 x N	>2.00 x N
CG PTT	Partial thromboplastin time	WNL	1.01-1.66 x N	1.67-2.33 x N	2.34-3.00 x N	>3.00 x N
CG OTH	Other*	None	Mild	Moderate	Severe	Life threatening
DENTITION (TEETH)						
DE DEC	Tooth decay*	None	Mild	Moderate	Severe	-
DE PAI	Toothache*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
DE OTH	Other*	None	Mild	Moderate	Severe	Life threatening
ENDOCRINE*						
EN AME	Amenorrhea	None	Irregular menses	≥3 months	-	-
EN CUS	Cushingoid	Normal	Mild	Pronounced	-	-
EN FLA	Hot flashes	None	Mild or <1/day	Moderate & ≥1/day	Frequent & interferes with normal function	-
EN GYN	Gynecomastia	Normal	Mild	Pronounced or painful	-	-
EN IMP	Impotence/Libido	Normal	Decrease in normal function	-	Absence of function	-
EN OTH	Other	None	Mild	Moderate	Severe	Life threatening
FLU-LIKE SYMPTOMS						
FL FEV of	Fever in absence of infection* (incl drug fever)	None	37.1-38.0°C 98.7-100.4°F	38.1-40.0°C 100.5-104.0°F	>40.0°C >104.0°F for <24hrs	>40.0°C (104.0°F) for >24hrs or fever accompanied by hypotension
Fever felt to be caused by <u>drug allergy</u> should be coded as ALLERGY (AL LER). <u>Non-allergic</u> drug fever (eg: as from biologics) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to <u>infection</u> , code INFECTION only (IN FEC or IN NEU).						
FL HAY nasal	Hayfever* (incl sneezing, stuffiness, post-nasal drip)	None	Mild	Moderate	Severe	-
FL JOI	Arthralgia* (joint pain)	None	Mild	Moderate	Severe	-
FL LET	Lethargy* (fatigue, malaise)	None	Mild, or fall of 1 level in performance status	Moderate, or fall of 2 levels in perf. status	Severe, or fall of 3 levels in perf. Status	-
FL MYA	Myalgia* (muscle ache)	None	Mild	Moderate	Severe	-
FL RIG	Rigors/Chills* (gr 3 incl cyanosis)	None	Mild	Moderate	Severe	-
FL SWE	Sweating* (diaphoresis)	None	Mild	Moderate	Severe	-
FL OTH	Other*	None	Mild	Moderate	Severe	Life threatening

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA

REVISED: 94-DEC-21

GRADE		0	1	2	3	4
GASTROINTESTINAL						
GI ANO	Anorexia*	None	Mild	Moderate	Severe	Dehydration
GI APP	Appetite increased*	None	Mild	Moderate	-	-
GI ASC	Ascites (non-malignant)*	None	Mild	Moderate	Severe	Life threatening
GI DIA	Diarrhea	None	Increase of 2-3 stools/day; or mild increase in loose watery colostomy output compared to pre-trt	Increase of 4-6 stools/day, or nocturnal stools; or moderate increase in loose watery colostomy output compared to pre-trt	Increase of 7-9 stools/day, or incontinence, malabsorption; or severe increase in loose watery colostomy output compared to pre-trt	Increase of ≥10 stools/day, or grossly bloody diarrhea; or grossly bloody colostomy output or loose watery colostomy output req parenteral support; dehydration
GI DPH	Esophagitis/dysphagia/odynophagia* (incl recall reaction)	None	Dys, or odyn, not req trt, or painless ulcers on esophagoscopy	Dys. or odyn. req trt	Dys. or odyn. Lasting >14 days despite trt	Dys, or odyn. With 10% loss of body wt, dehydration, hosp. Req
GI DRY	Mouth, nose dryness*	None	Mild	Moderate	Severe	-
GI FIS	Fistula (intestinal, esophageal, rectal)*	None	-	-	Req intervention	Req operation
GI GAS	Flatulence*	None	Mild	Moderate	Severe	-
GI HEA	Heartburn* (incl dyspepsia)	None	Mild	Moderate	Severe	-
GI HEM	Gastrointestinal bleeding*	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, >4 units transfusion per episode
Bleeding resulting from thrombocytopenia should be coded under BL HEM, not GI						
GI NAU	Nausea	None	Able to eat reasonable intake	Intake significantly decreased but can eat	No significant intake	-
GI OBS	Small bowel obstruction*	None	-	Intermittent, no intervention	Req intervention	Req operation
GI PAI	Gastrointestinal pain/cramping* (incl rectal pain)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
GI PRO	Proctitis (rectal)	None	Perianal itch, hemorrhoids	Tenesmus or ulcerations relieved with therapy, and fissure	Tenesmus or ulcerations or other symptoms not relieved with therapy	Mucosal necrosis with hemorrhage or other life threatening proctitis
GI STO	Stomatitis/oral	None	Painless ulcers, erythema, or mild soreness	Painful erythema, oedema, or ulcers but can eat	Painful erythema, oedema, or ulcers, and cannot eat	Mucosal necrosis and/or req parenteral or enteral support, dehydration
GI TAS	Taste, sense of altered*	None	Mild	Moderate	Severe	-
GI ULC	Gastritis/ulcer*	None	Antacid	Req vigorous medical management or non-surgical trt	Uncontrolled by medical management; req surgery for GI ulceration	Perforation or bleeding
GI VOM	Vomiting	None	1 episode in 24hrs	2-5 episodes in 24hrs	6-10 episodes in 24hrs	>10 episodes in 24hrs or req parenteral support, dehydration
GI OTH	Other*	None	Mild	Moderate	Severe	life threatening

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA

REVISED: 94-DEC-21

GRADE	0	1	2	3	4
GENITOURINARY					
GU BLA Bladder changes*	None	Light epithelial atrophy, or minor telangiectasia	Generalised telangiectasia	Severe generalised telangiectasia (often with petechiae) or reduction in bladder capacity (<15ml)	Necrosis, or contracted bladder (capacity <100ml), or fibrosis
GU CRE Creatinine	WNL	<1.5 x N	1.5-3.0 x N	3.1-6.0 x N	>6.0 x N
GU CYS Cystitis* (non-bacterial)	None	Mild symptoms req no intervention	Symptoms relieved completely with therapy	Symptoms not relieved despite therapy	severe (life threatening) cystitis
Urinary tract infection should be coded under infection, not GU					
GU FIS Fistula* (vaginal, vesicovaginal)	None	-	-	Req intervention	Req operation
GU FRE Frequency*	None	Freq of urination or nocturia twice pre-trt habit	Freq of urination or nocturia <hourly	Freq with urgency and nocturia \geq hourly	-
GU HEM Hematuria, bleeding per vagina	Neg	Micro only	Gross, no clots	Gross + clots	Req transfusion
Bleeding resulting from thrombocytopenia should be coded under BL HEM, not GU					
GU INC Incontinence*	None	Mild	Moderate	Severe	-
GU OBS Ureteral obstruction*	None	Unilateral, no surgery	Bilateral, no surgery req	Not complete bilateral, but stents, nephrostomy tubes or surgery req	Complete bilateral obstruction
GU PAI Genito-urinary pain (eg: dysuria, dysmenorrhea, dyspareunia)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
GU PRT Proteinuria	no change	1+ or <0.3g% or <3g/L	2-3+ or 0.3-1.0g% or 3-10g/L	4+ or >1.0g% or >10g/L	Nephrotic syndrome
GU VAG Vaginitis* (+/- vaginal discharge) (non-infectious)	None	Mild, no trt req	Moderate, relieved with trt	Severe, not relieved with trt	Life threatening
GU OTH Other*	None	Mild	Moderate	Severe	Life threatening
HEPATIC					
HP ALK Alk Phos or 5' nucleotidase	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP ALT Transaminase SGPT (ALT)	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP AST Transaminase SGOT (AST)	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP BIL Bilirubin	WNL	-	<1.5 x N	1.5-3.0 x N	>3.0 x N
HP CLI Liver (clinical)	No change from baseline	-	-	Precoma	Hepatic coma
HP LDH LDH*	WNL	≤ 2.5 x N	2.6-5.0 x N	5.1-20.0 x N	>20.0 x N
HP OTH Other*	None	Mild	Moderate	Severe	life threatening
Viral Hepatitis should be coded as infection rather than liver toxicity					
INFECTION					
IN FEC Infection	None	Mild, no active trt	Moderate, localised infect req active trt	Severe, systemic infect req parenteral trt, specify site	Life threatening sepsis, specify site
IN NEU Febrile neutropenia* Absolute gran. count <1.0 x 10 ⁹ /L, fever >38.5°C treated with (or ought to have been treated with) IV antibiotics	None	-	-	Present	-
Fever felt to be caused by <u>drug allergy</u> should be coded as ALLERGY (AL LER). <u>Non-allergic</u> drug fever (eg: as from biologics) should be coded under FLU-LIKE SYMPTOMS (FL FEV). If fever is due to <u>infection</u> , code INFECTION only (IN FEC or IN NEU)					

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA

REVISED: 94-DEC-21

GRADE	0	1	2	3	4
METABOLIC (SI UNITS)					
MT AMY Amylase	WNL	<1.5 x N	1.5-2.0 x N	2.1-5.0 x N	>5.1 x N
MT HCA Hypercalcemia	<2.64 mmol/L	2.64-2.88	2.89-3.12	3.13-3.37	>3.37
MT LCA Hypocalcemia	>2.10 mmol/L	2.10-1.93	1.92-1.74	1.73-1.51	≤1.50
MT HGL Hyperglycemia	<6.44 mmol/L	6.44-8.90	8.91-13.8	13.9-27.8	>27.8 or ketoacidosis
MT LGL Hypoglycemia	>3.55 mmol/L	3.03-3.55	2.19-3.02	1.66-2.18	<1.66
MT LKA Hypokalemia*	no change or >3.5 mmol/L	3.1-3.5	2.6-3.0	2.1-2.5	≤2.0
MT LMA Hypomagnesemia	>0.70 mmol/L	0.70-0.58	0.57-0.38	0.37-0.30	≤0.29
MT LNA Hyponatremia*	no change or >135 mmol/L	131-135	126-130	121-125	≤120
MT OTH Other*	None	Mild	Moderate	Severe	Life threatening
NEUROLOGIC					
NE CER Cerebellar	None	Slight incoordination, dysidiadochokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
NE CON Constipation	None or no change	Mild	Moderate	Severe, obstipation	Ileus >96hrs
NE COR Cortical (incl drowsiness)	None	mild somnolence	Moderate somnolence	Severe somnolence, confusion, disorientation, hallucinations	Coma, seizures, toxic psychosis
NE DIZ Dizziness* (incl light headedness)	None	Mild	Moderate	Severe (incl fainting)	-
NE EXT Extrapramidal / Involuntary movement*	None	Mild agitation (incl restlessness)	Moderate agitation	Tonicollia, oculogyric crisis, severe agitation	-
NE HED Headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	-
NE HER Altered hearing	None or no change	Asymptomatic, hearing changes on audiometry only	Tinnitus, symptomatic hearing changes not req hearing aid or trt	Hearing changes interfering with function but correctable with hearing aid or trt	Hearing changes or deafness not correctable
NE INS Insomnia*	None	Mild	Moderate	Severe	-
NE MOO Mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
NE MOT Motor	None or no change	Subjective weakness; no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
NE PAI Neurologic pain* (eg: jaw pain)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
NE PER Personality change*	No change	Change, not disruptive to pt or family	Disruptive to pt or family	Harmful to others or self	Psychosis
NE SEN Sensory	None or no change	Mild paresthesias, loss of deep tendon reflexes (incl tingling)	Mild or moderate objective sensory loss; moderate paresthesias	sensory loss or paresthesias that interfere with function	-
NE VIS Vision	None or no change	Blurred vision	-	symptomatic subtotal loss of vision	Blindness
NE OTH Other*	None	Mild	Moderate	Severe	Life threatening

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA

REVISED: 94-DEC-21

GRADE	0	1	2	3	4	
OCULAR						
OC CAT	Cataract*	None	Mild	Moderate	Severe	-
OC CJN	Conjunctivitis/ Keratitis	None	Erythema or chemosis not req steroids or antibiotics	Req trt with steroids or antibiotics	Corneal ulceration or visible opacification	-
OC DRY	Dry eye	Normal	Mild	Req artificial tears	Severe	Req enucleation
OC GLA	Glaucoma	No change	-	-	Yes	-
OC PAI	Eye pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	pain controlled with opioids	Uncontrollable pain
OC TEA	Tearing* (watery eyes)	None	Mild	Moderate	Severe	-
OC OTH	Other	None	Mild	Moderate	Severe	Life threatening
OSSEOUS (BONE)						
OS PAI	Bone pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
OS OTH	Other* (eg: avascular necrosis)	None	Mild	Moderate	Severe	Life threatening
OTHER						
OT OTH	Other	None	Mild	Moderate	Severe	Life threatening
For toxicities which do not have an existing code, but do fit into an existing toxicity category, use 'other' variable in the appropriate toxicity category. Only toxicities which do not fit into existing categories should be coded OTHER OTHER (OT OTH).						
PULMONARY						
PU CMD	Carbon Monoxide Diffusion Capacity (DLCO)*	>90% of pretreatment value	decrease to 76-90% of pre-trt	Decrease to 51-75% of pre trt	Decrease to 26-50% of pre-trt	Decrease to ≤25% of pre-trt
PU COU	Cough*	None	Mild	Moderate	Severe	-
PU EDE	Pulmonary Oedema*	None	-	Out-pat management	In-pat management	Req intubation
PU EFF	Pleural effusion* (non-malignant)	None	Mild	Moderate	Severe	Life threatening
PU FIB	Pulmonary fibrosis*	Normal	Radiographic changes, no symptoms	-	Changes with symptoms	-
PU HEM	Hemoptysis*	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, >4 units transfusion per episode
Bleeding resulting from thrombocytopenia should be coded under BL HEM, not PU						
PU HIC	Hiccoughs*	None	Mild	Moderate	Severe	-
PU PAI	Pulmonary pain*	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
PU PNE	Pneumonitis* (non-infectious)	Normal	Radiographic changes, symptoms do not req steroids	Steroids req	Oxygen req	Req assisted ventilation
PU SOB	Shortness of breath (SOB) (incl wheezing)	None or no change	Asymptomatic, with abnormality in PFT's	Dyspnea on significant exertion	Dyspnea at normal level of activity, apnea without cyanosis	Dyspnea at rest, apnea with cyanosis
PU VOI	Voice changes* (incl hoarseness, loss of voice)	None	Mild	Moderate	Severe	-
PU OTH	Other*	None	Mild	Moderate	Severe	Life threatening
Pneumonia is considered infection and not graded as pulmonary toxicity unless felt to be resultant from pulmonary changes directly induced by treatment						

NCIC CTG EXPANDED COMMON TOXICITY CRITERIA

REVISED: 94-DEC-21

GRADE	0	1	2	3	4
SKIN					
SK ALO	No loss	Mild hair loss	Pronounced or total head hair loss	Total body hair loss	-
SK CHA (photosensitivity)	None	Localised pigmentation changes	Generalised pigmentation changes or atrophy	Subcut fibrosis or localised shallow ulceration	Generalised ulcerations or necrosis
SK DES	None	Dry desquamation	Moist desquamation	Confluent moist desquamation	-
SK DRY	None	Mild	Moderate	Severe	-
SK FAC (facial)	None	Mild	Moderate	Severe	-
SK HEM	None	Mild, no transfusion	Gross, 1-2 units transfusion per episode	Gross, 3-4 units transfusion per episode	Massive, >4 units transfusion per episode
Bleeding resulting from thrombocytopenia should be coded under BL HEM, not SK					
SK LTO (reaction at IV site)	None	Pain	Pain and swelling, with inflammation or phlebitis	Ulceration	Plastic surgery indicated
SK NAI	None	Mild	Moderate	Severe	-
SK PAI (incl scalp pain)	None	Pain, but no treatment req	Pain controlled with non-opioids	Pain controlled with opioids	Uncontrollable pain
SK RAS (not due to allergy) (incl recall reaction)	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or papular eruption or erythema with pruritus or other associated symptoms	Generalised symptomatic macular, papular, or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis
SK OTH	None	Mild	Moderate	Severe	Life threatening
WEIGHT					
WT GAI	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	-
WT LOS	< 5.0%	5.0-9.9%	10.0-19.9%	≥ 20.0%	-

Any toxicity which causes death should be given Grade 5

* Denotes NCIC specific criteria.

*A phase II study VEPEMB
In patients with Hodgkin's Lymphoma
Aged 60 years and older*

QUESTIONNAIRE

QUALITY OF LIFE

Dear Patient

We would like to ask for your co-operation and help. Great improvements in the treatment of your illness have been achieved over the past twenty years so that most patients can be cured today. However, over recent years more and more attention is being given to finding new treatments that have fewer side-effects.

Questions were raised about how the *Quality of Life* of patients is affected by the disease and the treatment and which measures they use to help overcome these difficulties. Furthermore, more information is needed about how patients cope with their illness and the effects of treatment, in order to make treatment more successful. It is of course essential that patients are able to cope with the disease and side effects of treatment and are able to return to normal life as soon as possible. Until now very little was known about general and specific physical, psychological and emotional experiences of patients who had radiotherapy and/or chemotherapy for Hodgkin's disease.

In trying to make a significant step forward regarding these points, a questionnaire has been designed to obtain the most relevant information from the patient's own point of view. The intention is to collect this information repeatedly during at least five years of follow-up. This information can be of great help to improve understanding of points in time when particular problems arise. In future this information could be used to develop more precisely measures of help and support and to contribute to further development of the medical treatment itself so that as few as possible negative effects occur.

Your help in participating in this investigation will, therefore, particularly influence the treatment of future patients suffering from Hodgkin's disease but also might be of help for yourself when speaking with your physician about your own situation and possible problems.

We would, therefore, like to ask you to fill in this questionnaire at the follow-up visits. Should, by mistake, the questionnaire not be handed out (or sent) to you, please help by reminding your physician or nurse about it.

For your own information, please note that the problems and side-effects which are mentioned in the questionnaire might bother a number of patients but are by no means likely or expected to occur in all patients. All the information you provide will of course remain confidential and for scientific analysis the forms will be used anonymously only.

Thank you very much for your help and co-operation in this important investigation.

Please answer all of the questions yourself, by circling the number that best applies to you. There are no 'right' or 'wrong' answers.

Please fill in your initials: _____

Female

Your birth date (Day, Month, Year) _____

Male

Today's date (Day, Month, Year) _____

Currently employed Yes No

Profession / work _____

		Not At All	A Little	Quite A bit	Very Much
1	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2	Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3	Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4	Do you need to stay in a bed or in a chair during the day?	1	2	3	4
5	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
	DURING THE PAST WEEK	Not At All	A Little	Quite A bit	Very Much
6	Were you limited in doing either your work or other daily activities?	1	2	3	4
7	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8	Were you short of breath?	1	2	3	4
9	Have you had pain?	1	2	3	4
10	Did you need to rest?	1	2	3	4
11	Have you had trouble sleeping?	1	2	3	4
12	Have you felt weak?	1	2	3	4
13	Have you lacked appetite?	1	2	3	4
14	Have you felt nauseated?	1	2	3	4
15	Have you vomited?	1	2	3	4

		Not At All	A Little	Quite A bit	Very Much
16	Have you been constipated?	1	2	3	4
17	Have you had diarrhoea?	1	2	3	4
18	Were you tired?	1	2	3	4
19	Did pain interfere with your daily activities?	1	2	3	4
20	Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21	Did you feel tense?	1	2	3	4
22	Did you worry?	1	2	3	4
23	Did you feel irritable?	1	2	3	4
24	Did you feel depressed?	1	2	3	4
25	Have you had difficulty remembering things?	1	2	3	4
26	Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27	Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28	Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4
29	Have you had a dry mouth?	1	2	3	4
30	Have you had tingling (“pins and needles”) in your hands or feet?	1	2	3	4
31	Have you had infections? (Flu, chest infection, skin infection etc)	1	2	3	4
32	Has your interest in sex decreased?	1	2	3	4
33	Has your sexual activity decreased?	1	2	3	4
34	Has your pleasure or satisfaction from sex decreased?	1	2	3	4
35	Were you worried that you may not be able to have children anymore?	1	2	3	4

For the following questions, please circle the number between 1 and 5 that best applies to how you have been feeling lately.

		Yes, that is true				No that is not true
36	I feel fit.	1	2	3	4	5
37	Physically, I feel only able to do a little.	1	2	3	4	5
38	I feel very active.	1	2	3	4	5
39	I feel like doing all sorts of nice things.	1	2	3	4	5
40	I feel tired.	1	2	3	4	5
41	I think I do a lot in a day.	1	2	3	4	5
42	When I am doing something, I can keep my thoughts on it.	1	2	3	4	5
43	Physically, I can take on a lot.	1	2	3	4	5
44	I dread having to do things.	1	2	3	4	5
45	I think I do very little in a day.	1	2	3	4	5
46	I can concentrate well.	1	2	3	4	5
47	I am rested.	1	2	3	4	5
48	It takes a lot of effort to concentrate on things.	1	2	3	4	5
49	Physically, I feel I am in a bad condition.	1	2	3	4	5
50	I have a lot of plans.	1	2	3	4	5
51	I tire easily.	1	2	3	4	5
52	I get little done.	1	2	3	4	5
53	I don't feel like doing anything.	1	2	3	4	5
54	My thoughts easily wander.	1	2	3	4	5
55	Physically, I feel I am in an excellent condition.	1	2	3	4	5

For the following questions, please circle the number between 1 and 7 that best applies to you.

		Very poor						Excellent
56	How would you rate your overall <i>physical condition</i> during the past week?	1	2	3	4	5	6	7
57	How would you rate your overall <i>emotional condition</i> during the past week?	1	2	3	4	5	6	7
58	How would you rate your overall <i>health</i> during the past week?	1	2	3	4	5	6	7
59	How would you rate your overall <i>quality of life</i> during the past week?	1	2	3	4	5	6	7

The following questions refer to the time period from diagnosis and start of treatment until today.

		Not At all						Very Much
60	How much did the disease treatment affect your self-confidence?	1	2	3	4	5	6	7
61	How much of an emotional burden was the disease and treatment for you?	1	2	3	4	5	6	7
62	Has your relationship with your partner changed?	1	2	3	4	5	6	7
In which respect?								
63	How much did the disease and treatment affect your sex life?	1	2	3	4	5	6	7
In which respect?								
64	In general, how difficult was the disease and treatment for you?	1	2	3	4	5	6	7
In which respect?								

		Yes, Definitely						Under no Circumstances
65	From your own experience, would you recommend this form of treatment to a close friend or relative with the same disease?	1	2	3	4	5	6	7
66	Looking back, would you again agree to have the treatment you received?	1	2	3	4	5	6	7
67	In which regard would you decide differently today?	(regarding?)						
68	What has been the most difficult consequence of your treatment?							
69	Was something important not mentioned?							

Please check, to ensure you answered all the questions
Thank you very much for your help and co-operation

Patient Information Sheet
(Hospital Headed Paper)

A Phase II study of efficacy of VEPEMB in older patients with Hodgkin's Lymphoma

You have been diagnosed with Hodgkin's lymphoma and your doctor believes that you will benefit from treatment with chemotherapy. We would like to ask you to consider taking part in a research study which hopes to confirm results from elsewhere that a particular mixture of drugs might be the best for older patients with Hodgkin's lymphoma .

Before you decide whether to take part it is important for you to understand why the research is being done. Please take time to read the following information carefully and to discuss it with friends, relatives and your GP if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Consumers for Ethics in Research (CERES) publish a leaflet entitled Medical Research and you. This leaflet gives information about medical research and looks for some questions you may want to ask. A copy may be obtained from CERES, P.O. Box 1365, London, N16 0BW.

Thank you for reading this.

What is the purpose of the study?

Hodgkin's lymphoma is an unusual cancer in that it is usually found in younger patients. However about one in five of patients who develop this disease are over 60 years of age. Over the last twenty years younger patients have had improved survival due to being able to tolerate more intensive treatment but older patients are usually excluded from studies of these treatments and therefore the manner in which they are treated and the clinical outcome is not well described.

The reasons for this lack of tolerance of intensive treatment is probably due to a combination of factors including the difficulty of completing all the planned courses of treatment on time because of problems with the treatment due to the increased toxicity of the drugs in older patients.

Worldwide, conventional treatment for Hodgkin's lymphoma is to give consecutive cycles of chemotherapy (ABVD) involving four drugs (adriamycin, bleomycin, vinblastine and dacarbazine) but this can be very difficult to give in older patients.

Since 1996, The Italian Intergroup Study Group for Lymphoma has treated 100 patients aged > 65 years with a combination therapy, VEPEMB, this includes 7 drugs (vinblastine, cyclophosphamide, procarbazine, prednisolone, etoposide, mitoxantrone and bleomycin) given in part by injection into a vein and in part by mouth. This new combination appears to be well tolerated and to give similar results to the ABVD combination when compared to patients treated with this combination historically.

In order to confirm that VEPEMB is associated with less toxicity problems and gives improved results in older patients we have proposed the current study.

Secondly, as it can be difficult to diagnose this particular form of lymphoma, an important part of this study is to investigate tumour specimens, which are routinely collected, using new techniques. From this we hope to learn more about the characteristic features of this disease, and whether these features can be used to identify groups of patients with a better or worse than average chance of cure. This will help us decide whether some groups of patients should be treated differently in future.

Another part of the study will address the problem of whether it is possible to predict patients who will not tolerate the treatment.

Why have I been chosen?

You have been chosen to enter this study as the pathologist at your local hospital has made a diagnosis of Hodgkin's lymphoma on a biopsy specimen and you are aged ≥ 60 years.

Do I have to take part?

It is up to you to decide whether or not to take part, and it is possible for you to agree to take part in the clinical study, but not the pathology sub-study if you wish. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide not to take part you will receive standard treatment for your disease and the standards of your care will not be affected.

If you do decide to take part you are still free to change your mind at any time, without giving a reason.

What will happen to me if I take part?

Whether or not you take part in this study the treatment you receive will be very similar. Involvement in the study will not involve any extra visits or time in hospital, therefore your expenses in travelling from home to the hospital will not be reimbursed.

Before starting treatment it will be necessary for your doctor to establish how advanced your Hodgkin's lymphoma is, we call this "staging". This will involve routine blood tests, in particular to check your kidney and liver function, CT scans and if indicated a bone marrow biopsy.

Data on the treatment you receive and your progress will be reported in confidence to the study organisers, the SHIELD (Study of Hodgkin's lymphoma In the Elderly/Lymphoma Database) Study Unit, who will put this together with data from all the other patients in the study, without identifying anyone individually.

Analysis of Samples Before Treatment

With your permission we would like to send some of the tumour sample collected routinely by your hospital to be examined by an expert pathologist at the Pathology Department, Royal Victoria Infirmary, Newcastle upon Tyne (this is the "pathology sub-study"). As part of this study, new techniques will be used to examine tumour cells in more detail. This will not affect your treatment in any way (and you will not benefit financially), but by collecting similar information on lots of patients we may be able to identify features which allow us to predict more accurately how patients will respond to different treatments in the future. The tumour sample would be anonymised, but would be identified by a numerical code so that when, and only when, the pathologist's report on the sample is sent to the study organisers (the SHIELD Study Group) they will be able to link the pathology details to details of your treatment and progress. When the study is completed, the biopsy sample will be returned to your local hospital.

We would also like to ask your permission to take a serum blood sample at diagnosis to be stored in Newcastle for possible use in future projects relating to the diagnosis and treatment of Hodgkin's

lymphoma, as new techniques become available. These may be carried out by researchers other than those in Newcastle. This blood sample may be fully used in the research or in subsequent research and will be considered as a 'gift' from you to the research team. No one involved with this study would benefit financially if this were to happen. All further research using such stored samples will require approval from an appropriate Research Ethics Committee.

What is the drug or procedure that is being tested?

Depending on how advanced your disease is you will be given a different number of courses of your chemotherapy (VEPEMB). In "early stage" disease (i.e. disease is localised) you will receive 3 courses of treatment followed by radiotherapy to the areas originally involved.

If your disease is more extensive "advanced stage" you will be given 6 courses of treatment and (possibly) radiotherapy to any disease that remains or sites of initial bulky disease.

Each course of treatment lasts 4 weeks and you will need to attend the hospital weekly during the treatment phase. Your treatment will take approximately 5 months if you have early stage disease and 9 months if it is more advanced. These treatments are normally given on an outpatient basis. The treatment is complicated and will be discussed with you in detail by one of the clinical team involved in your care.

What are the side effects of any treatment received when taking part?

As with all chemotherapy, your treatment will result in side effects. The drugs can cause nausea and vomiting but you will be given treatment to prevent this. You are likely to lose your hair but this will be temporary and we can provide a wig. The most important clinical side effects involve those affecting your blood. Your white cells (which fight infection) can become very low and you will be given prophylactic antibiotics if this occurs. If your haemoglobin level drops (due to decreased numbers of red cells) you may need a blood transfusion and, in some patients, your platelets (which help blood clot) may be low and you may require platelet transfusions.

Additional common side effects are tiredness, a sore mouth related to the treatment and tingling in the fingers and toes. More details will be provided of this by your doctor and nursing staff. Once chemotherapy is completed virtually all these side effects completely disappear.

What are the alternatives for diagnosis or treatment?

Hodgkin's lymphoma is a cancer for which chemotherapy would always be the treatment of choice, giving the maximum chance of cure. Chemotherapy used for the younger patients (ABVD) is too toxic for older people. However, the seven drugs used in the VEPEMB schedule are well known and have been sequenced to allow best effect, with as little side-effects as possible. We are not making any comparisons of treatments in this study but aiming to assess the protocol in a large number of patients (150), in an organised way.

What are the possible advantages and risks of taking part?

Although Hodgkin's lymphoma is a cancer which, untreated, usually causes death within a period of months, drug treatment like that recommended in this study results in cure in over half of patients. Combination chemotherapy strongly recommended, whether or not you take part in this study. To achieve these cure rates, we have to give fairly intensive chemotherapy, which does have side effects as described above; however you will be monitored closely throughout your treatment so that any side effects can be treated promptly.

Male patients should use contraception (if relevant) during the course of this study as it is possible the treatment may interfere with the normal functioning of male sperm.

What are the possible benefits of taking part?

It is expected that receiving treatment with VEPEMB will cure a substantial proportion of patients with this form of lymphoma. We hope that the results of this study will mean that in future patients will receive effective, but perhaps less toxic treatment than before.

Accurate diagnosis of this disease is extremely important. The pathology part of the study will not benefit you directly but we hope it will benefit future patients with this condition by giving them better information on their chances of cure, and in helping to decide the most appropriate treatment.

What if new information becomes available?

In the event that a new treatment for Hodgkin lymphoma becomes available which is of advantage to you this will of course be shared with you. If a new form of therapy would be beneficial to you then this will be discussed with you and it would be possible for you to withdraw from the present study. If you chose to continue, you may be asked to sign an updated consent form.

What happens when the research study stops?

Since the study does not include new drugs and all the drugs are available for routine care, it is anticipated that the treatment schedule may become a standard treatment for Hodgkin's lymphoma in elderly patients. If it does become a standard treatment then it may be used for comparison if a new treatment were to come along in the future.

What if something goes wrong?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you. If you are harmed by taking part in this research project, there are no special compensation programmes. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it.

What do I have to do?

The information about the treatment you received for the study will be collected from your doctor. We do not know if participation in this study will benefit you but we hope it will benefit patients in the future by giving better information on their chances of cure and helping to decide on the most appropriate treatment. However, we would ask that you will be involved in the study by filling in a questionnaire about how you feel.

It is becoming increasingly important for doctors to be able to compare the side effects of different treatments and also to learn how patients are coping with their disease and treatment (we call this "Quality of Life" assessment). A questionnaire has been designed to obtain this information for the patient's point of view. Our intention would be to collect this information four times: before treatment, immediately after treatment has finished, 1 year after diagnosis and 5 years after diagnosis. In future this information could be used to develop support systems for patients as well as influencing treatment.

We would ask you to fill in the questionnaire both before treatment and at the follow up visits. If the questionnaire is not given to you, please help by reminding your doctor or nurse about it.

Will my taking part in this study be kept confidential

If you consent to take part in a research study such as this one, relevant aspects of your medical records will be sent, in confidence, to the SHIELD Study Group Unit (SSTU). They are registered under the Data Protection Act to hold patient information in secure storage, to be accessed only by appropriate staff involved with this study. Once registered in this study, the SSTU will give your

doctor an identification number which uniquely identifies you, so that your full name need not be kept on the main study database. Similarly, with your agreement, some small pathology specimens will be sent to the Department of Pathology in Newcastle. Your name and address will be removed from such specimens so that you will not be identifiable other than to the SSTU, and all information from the study will be kept strictly confidential. No individual patients will be identified when the results of the study are published. Your General Practitioner will however be informed of your participation in the study.

What will happen to the results of the research study?

Approximately one to two years after the study has been completed (it is anticipated this will take at least 3-4 years) the results will be published in a recognised medical journal. The results will be available to you at this time as will a copy of the published results if you would like this. You will not be identified in any report or publication.

Who has reviewed the study?

A Multi-centre Research Ethics Committee will have approved this study, as will the Local Research Ethics Committee for your hospital.

Who is the organising this research?

The study is being organised by the SHIELD Study Group. Your clinical care will be paid for by the usual National Health Service mechanism. Your doctor will not be paid for including you in this study.

Contact for further information

Should have worries or concerns about your treatment we recommend that you contact _____ who can be contacted on the telephone number _____

Thank you for considering taking part in this study.

PLEASE NOTE: Please let your Physician know if you have any eyesight problems which prevent you for reading this document clearly. Arrangements can be made to have it read to you in an appropriate and understandable way. Similarly, if English is your second language, an interpreter can be provided

Participant Consent Form

A phase II study VEPEMB in patients with Hodgkin Lymphoma aged \geq 60 years.

The participant should complete the whole of this sheet him or herself.
(please write your initials in the following boxes if you agree with the statement).

Please
initial here



1.	I confirm that I have read and understood the information sheet dated for the above study and have had the opportunity to ask questions.	
2.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without it affecting my medical care or legal rights.	
3.	I understand that sections of any of my medical notes may be looked at by responsible individuals from the study team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records and review the pathology samples on what diagnosis was made. I agree to have a blood sample stored so further research into Hodgkin's disease can be carried out.	
4.	I agree to my General Practitioner being informed of my participation in the study.	
5.	I agree to take part in the above study.	

Name of Patient

Date

Signature

Name of Person taking consent
(if different from researcher)

Date

Signature

Researcher

Date

Signature

1 copy for patient; 1 copy for researcher; 1 copy to be kept with hospital notes.

(Hospital Headed Paper)

GP Letter/referring Consultant

Dear Dr

A phase II study VEPEMB in patients with Hodgkin Lymphoma aged \geq 60 years.

Your Patient:.....

(D.O.B.:/..../....)

has recently been found to have Hodgkin's lymphoma, for which combination chemotherapy has been recommended. They have kindly agreed to take part in a phase II study that uses the standard treatment VEPEMB (Vinblastine, Cyclophosphamide, Prednisolone, Procarbazine, Mitoxantrone, Etoposide and Bleomycin).

You will be kept up to date with your patient's progress but if you could have any concerns or questions regarding this study please contact the responsible physician:

Dr at Hospital.

Tel: at any time.