Intergroup Study (EORTC protocol 20012)
(EudraCT number 2004-001558-10)

BEACOPP (4 cycles escalated + 4 cycles baseline) versus ABVD (8 cycles) in stage III & IV Hodgkin’s lymphoma

Coordinating Group: EORTC Lymphoma Group
Collaborative Groups:

Australasian Lymphoma Leukemia Group (ALLG)
National Cancer Research Institute Lymphoma Group (NCRI LYG)
Grup per l’Estudi dels Limfomes de Catalunya i Balears (GELCAB)
National Cancer Institute of Canada (NCIC)
Nordic Lymphoma Group (NLG)

Study Chairman: Dr. Patrice Carde (EORTC)
Study Co-Chairman: Dr. Marine Divine (GELA)

Warning:
This is an Intergroup study coordinated by the EORTC. The present protocol is written according to the EORTC procedures, and is fully applicable to all EORTC investigators (with the exception of other collaborative groups' specific appendices).

The scientific section (chapters 1 to 13) and the publication policy (chapter 14) are also fully applicable to investigators from all other collaborative groups. For administrative matters, non EORTC investigators should refer to their Group specific appendix, that will supersede the contents of chapters 15 to 22.

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1 Background and introduction

According to most investigators, the standard chemotherapy regimen in patients with advanced Hodgkin’s Lymphoma is ABVD.

Two successive large randomized CALGB phase III studies showed no advantage of alternating regimens (like COPP/ABVD, MOPP/ABVD, MOPP/ABV) over ABVD, although they proved superior to MOPP. In the first trial (CALGB 1982), ABVD matched the results achieved with MOPP/ABV, both regimens surpassing those of MOPP (Ref. 9). Canadian investigators participated in the second recent large trial (CALGB/SWOG/ECOG/NCIC 8952 trial; n=856), where ABVD matched the results achieved with MOPP/ABV (Ref. 24). ABVD was therefore recommended instead of MOPP/ABV for its lower toxicity, including myelodysplasia (MDS) & acute myeloid leukemia (AML). Unpublished updates of these 2 trials confirm the earlier results. Similarly, the BNLI’s ChlVPP/EVA proved superior to MVPP and VAPEC-B, but not to ABVD (Ref. 48).

Dose impacts clearly on FFP and OS outcome: definition of the dose-intense experimental arm.

Dose impact (Ref. 29) has been suggested in a number of retrospective studies (Ref. 3, Ref. 11, Ref. 43, Ref. 52) and in large phase II studies (Ref. 31, Ref. 63). However, consolidative dose intensification with autologous hematopoetic transplant in high-risk CR/Cru (i.e. PR>75%) patients did not provide any benefit in a large randomized trial (Ref. 27). Increased COPP/ABVD regimen was compared prospectively to a standard COPP/ABVD (supposed to be equivalent to MOPP/ABV or MOPP/ABVD). The escalated regimen resulted in higher CR rate (Ref. 30).

Adaptations of increased COPP/ABVD regimen (Ref. 63) were tested in the large 3-arm phase III HD-9 trial, comparing baseline and escalated BEACOPP to the regular COPP/ABVD (Ref. 17). The escalated BEACOPP provided a higher 3y Freedom From Treatment Failure (FFTF) / Event Free Survival (EFS). At 40 months, the FFTF/EFS was 89% with escalated BEACOPP versus 79% with BEACOPP baseline and 70% with standard COPP/ABVD (0.05 for each comparison). The overall survival differences were significantly better in the 2 combined BEACOPP arms: 92% and 91% with escalated BEACOPP and BEACOPP baseline respectively versus 86% with COPP/ABVD. The number of deaths was 32/463 versus 41/457 versus 46/263, respectively (Ref. 17). Early progressions and secondary NHL were rarer in the escalated arm. No FFTF advantage was observed for the patients within the age category 60 to 65 years old.

However, immediate toxicity is worth consideration: 25% of cycles with anemia and 69% of patients with grade 3-4 anemia. In addition, secondary myelodysplasia and acute myeloid leukemia (MDS/AML) is more frequent in the escalated arm (1.8% with standard error 0.8% after 3 years) and may spoil the results (Ref. 10). These data have been updated with additional follow-up September 2001 Köln meeting: 8 AML/1 MDS was observed in 460 escalated BEACOPP patients (1.9%) versus 2 AML/MDA in 457 baseline BEACOPP patients (0.4%) versus 0/263 in standard arm (Ref. 17). The early occurrence and genetic characteristics of these AML suggest that they may be etoposide-induced. However, no additional AML/MDS has been observed in the last 18 months (communication ASH 2001).

The final data for this trial was presented during the 22-25 September 2001 Köln meeting. It was demonstrated that the 5y FFTF remained highly significant (69% for the standard treatment, 76% for the baseline BEACOPP, & 87% for the escalated BEACOPP) while the survival difference between the COPP/ABVD & escalated BEACOPP arms (83% & 91%, respectively) became also significant (Ref. 18).
The ongoing HD-12 trial of the German Hodgkin Study Group for advanced HD aims to keep optimal control with reduced toxicity by comparing the experimental BEACOPP escalated x 4 + BEACOPP baseline x 4 (+/- RT) arm to the previous GHSG baseline BEACOPP escalated x 8 (Ref. 17). Thus, the cumulative etoposide dose would be 25% reduced from 4.8 g/m² down to 3.6 g/m². For these reasons, the experimental arm is also the one retained for the present Intergroup study.

Current experience of the Intergroup.

In the H89 study by the GELA comparing MOPP/ABV vs. ABVPP, 62% 5y EFS was achieved in the 559 eligible patients (Ref. 28).

In the H3-4 study by the EORTC (Trial 20884 on adjuvant radiotherapy vs. control on patients treated with MOPP/ABVD), 82% 5y EFS (84% at 3y) and 88% 3y OS was achieved in the overall group of 678 patients enrolled. Following the first results (Ref. 50), there were no differences in EFS and OS between the group of patients with CR4 or CR6 (randomized for further RT or control) and those with PR6 (almost systematically treated with salvage consolidative RT).

In recent years, ABVD x8 cycles +/- RT was given in 115 patients in the CALGB 8251 study and in 428 patients in the CALGB 8952/SWOG/ECOG/NCIC study. It provided at 5 year FFS 61% & OS 73% (Canellos NEJM 327: 1478-84, 1992) in the first trial and a FFS 65% & OS 87% (Duggan Proc. ASCO 16: 12a (No. 43), 1997) in the second. These results are very similar to those observed either with COPP/ABVD x8 + RT (HD-3, HD-6 & HD-9 GHSG trials) or with MOPP/ABV (in the randomized CALGB 8952/SWOG/ECOG/NCIC study and in the H89 study quoted above. All these data concur to suggest that escalated BEACOPP is superior, except that the results with MOPP/ABV in the EORTC 20884 study are better than the others: in all 736 patients enrolled EFS was at 6 year 77% and OS 82% (Raemaekers ASH 2001); they match those of BEACOPP baseline (5 year EFS 76%, OS 87%) and are not so inferior to those of escalated BEACOPP (5 year EFS 88%, OS 91% Diehl Bonnadonna lecture Köln 2001). This is the justification of the present trial, in view of toxicities brought up by the escalated BEACOPP.

Prognostic stratification for trial eligibility.

Prognostic factors have recently been re-assessed through the effort of the International Prognostic Factor Project on Advanced Hodgkin’s disease (IPFPAHD) in almost 5000 patients. “Advanced” HD represented stages III & IV patients plus stages I & II patients already selected for “unfavorable” characteristics (13% of total). In this analysis, 7 adverse factors were identified:

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>p value</th>
</tr>
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<tbody>
<tr>
<td>Age ≥ 45</td>
<td>.0010</td>
</tr>
<tr>
<td>Sex = male</td>
<td>.0012</td>
</tr>
<tr>
<td>Stage IV</td>
<td>.0112</td>
</tr>
<tr>
<td>WBC ≥ 15*10⁹/l</td>
<td>.0013</td>
</tr>
<tr>
<td>Lymphocyte count &lt; .6*10⁹/l or &lt; 8% WBC</td>
<td>.0019</td>
</tr>
<tr>
<td>Albumin &lt; 4 g/dl</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Hemoglobin &lt; 10.5 g/dl</td>
<td>.0056</td>
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### PRONOSTIC SCORE

<table>
<thead>
<tr>
<th>Number of Adverse Prognostic Factors</th>
<th>Patients (%)</th>
<th>5 year-FFP (%)</th>
<th>5 year-Survival (%)</th>
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<tbody>
<tr>
<td>0</td>
<td>7</td>
<td>84</td>
<td>89</td>
</tr>
<tr>
<td>1</td>
<td>22</td>
<td>77</td>
<td>90</td>
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<td>29</td>
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<td>60</td>
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<tr>
<td>4</td>
<td>12</td>
<td>51</td>
<td>61</td>
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<tr>
<td>5+</td>
<td>7</td>
<td>42</td>
<td>56</td>
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Hasenclever NEJM 339 (Ref. 35), 1506-1515, 1998

Only patients with the IPS ≥3 will be enrolled in this Intergroup trial (EORTC trial 20012); for GELA investigators: for patients with the IPS <3 see Group Specific Appendix, the chapter about the Group specific scientific matters.

The repartition of IPS was assessed in the IPFPAHD series (Ref. 35), the HD-9 GHSG series (Diehl, interim analysis 6/2000), the EORTC series and the GELA H-89 series (Ref. 28).

### The repartition of the IPS in different series (% of patients)

<table>
<thead>
<tr>
<th>IPS/Series</th>
<th>IPFPAHD</th>
<th>GHSG HD-9</th>
<th>EORTC 20884</th>
<th>GELA H-89</th>
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<tr>
<td>0-2</td>
<td>58</td>
<td>57</td>
<td>46</td>
<td>41</td>
</tr>
<tr>
<td>≥3</td>
<td>42</td>
<td>43</td>
<td>54</td>
<td>59</td>
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Note that in the 20884 and H-89 studies, contrary to the IPFPAHD and HD-9 series, more than 50% of patients were classified as IPS ≥3 (H-89: calculated for the 266 M/A patients).

When the IPS is applied to the IPFPAHD series, to the 3 GHSG HD-9 trial arms, to the EORTC H3-4 trial and to the GELA trial, the following results are observed with standard chemotherapy regimens (+/- radiotherapy), respectively:

#### % of patients with 3 y FFTF and OS in the IPFPAHD series compared to EORTC, GELA and GHSG series.

<table>
<thead>
<tr>
<th>IPS series</th>
<th>GHSG HD-9</th>
<th>EORTC 20884</th>
<th>GELA H-89</th>
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<tr>
<td>C-A</td>
<td>B-base</td>
<td>B-esc.</td>
<td></td>
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<tr>
<td>262 Pts</td>
<td>405 Pts</td>
<td>403 Pts</td>
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#### % of patients with 3 y FFTF (5y EFS for H-89)

<table>
<thead>
<tr>
<th>IPS</th>
<th>74</th>
<th>73</th>
<th>81</th>
<th>92</th>
<th>90</th>
<th>(85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPS 3+</td>
<td>55</td>
<td>64</td>
<td>78</td>
<td>84</td>
<td>76</td>
<td>(65)</td>
</tr>
<tr>
<td>all patients</td>
<td>66</td>
<td>69</td>
<td>79</td>
<td>88</td>
<td>84</td>
<td>(72)</td>
</tr>
</tbody>
</table>

#### % of patients with 3 y OS (5y OS for H-89)

<table>
<thead>
<tr>
<th>IPS</th>
<th>86</th>
<th>91</th>
<th>92</th>
<th>94</th>
<th>93</th>
<th>(96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPS 3+</td>
<td>70</td>
<td>77</td>
<td>87</td>
<td>89</td>
<td>82</td>
<td>(69)</td>
</tr>
<tr>
<td>all patients</td>
<td>78</td>
<td>86</td>
<td>90</td>
<td>91</td>
<td>89</td>
<td>(80)</td>
</tr>
</tbody>
</table>

misc. CT = miscellaneous chemotherapy; C-A = COPP-ABVD; B-base = BEACOPP-baseline; B-esc. = BEACOPP-escalated; M/A = MOPP/ABV
Adjuvant irradiation (RT).

The benefit of adjuvant irradiation is debated. A meta-analysis on 16 comparative trials failed to demonstrate any advantage of combined CT & RT over CT alone, according to Barber et al. (Ref. 26). For patients who attain a CR after 6 cycles, any type of consolidation is beneficial (Ref. 28). Consolidative CT matches consolidative (sub)total irradiation [(S)TNI] in the GELA H-89 protocol (Ref. 28). The potential benefit of RT decreases when CT dose increases (German study), but its toxicity is likely to persist. Conversely, in patients who achieve an apparent PR after 6 cycles of CT, RT given to involved sites provides FFP rates that match those of CR patients after 6 cycles (Ref. 49, Ref. 50).

The most recent meta-analysis does not provide arguments in favor (nor against) the use of irradiation, but warns about late toxicity (Ref. 42).

The EORTC 20884 randomized study asks the question of adjuvant involved field irradiation (IFRT) versus control in patients who achieved a CR after a total of 6 or of 8 cycles. After a median follow-up of 6 years, the 5y EFS was 82% vs. 79% and overall survival was 89% vs. 85% in the control and IF RT arms and respectively (P = 0.05) (Ref. 51).

At this time, a consensus is achieved in all groups participating to the Intergroup trial (EORTC trial 20012), to consider that standard treatment (control arm) will rely on 8 cycles of ABVD with no RT for patients who achieve CR/CRu (PR 75%) after 6 cycles.

Conclusion.

The present study is proposed because results obtained with escalated BEACOPP in terms of EFS, overall survival, and low rate of early failures are impressively superior to those achieved with standard treatment, of the type of COPP/ABVD or ABVD. Moreover, this led the GHSG to stop their study earlier than planned. However, because of toxicity, and the risk of secondary leukemia, a study is mandatory to confirm these results. The implication for the future treatment of Hodgkin’s disease can be profoundly modified by the present study.

2 Objectives of the trial

2.1 General objectives

The present proposition is to assess whether treatment with 4 cycles of BEACOPP at the escalated dose followed by 4 cycles of BEACOPP at the baseline dose (GHSG regimen) improves event free survival when compared to the 8 cycles of the standard ABVD regimen in patients with measurable stage III or IV Hodgkin’s disease, with an International Prognostic Score (IPS) of 3 or higher (Ref. 35)

GELA investigators: for the patients with the IPS <3 see Group Specific Appendix (the chapter about the Group specific scientific matters).

2.2 End-points

The primary end point is Event-Free-Survival (EFS), also called Time to Treatment Failure or Freedom From Treatment Failure (FFTF). For this end-point, an "event" is defined as early discontinuation of protocol treatment, absence of CR after 8 cycles, relapse, progression or death. This is further detailed in the chapter on "evaluation criteria"
The secondary endpoints are: complete response (CR), disease free survival (DFS) in CR patients, overall survival (OS), quality of life (QoL), occurrence of second malignancies and cost-effectiveness.

The evaluation of response is done according to Response Evaluation Criteria for Hodgkin's Lymphoma (see chapter 7.2.)

3 Patient selection criteria

3.1 Patients Inclusion criteria:
♦ histologically documented Hodgkin’s lymphoma/disease, except for the subtype lymphocyte predominant, nodular type (nodular paragranuloma)
♦ clinical stage III or IV
♦ presence of at least one bi-dimensionally measurable target lesion, as defined in chapter 7.2.; patients with extranodal disease only will be eligible if they have at least one bi-dimensionally measurable extranodal lesion. Patients with no nodal or visceral measurable disease CANNOT be included.
♦ patients with an International Prognostic Score (IPS) ≥3

IPS is defined as the number of the following adverse factors:

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
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</tr>
<tr>
<td>Sex</td>
<td>= male</td>
</tr>
<tr>
<td>Stage</td>
<td>IV</td>
</tr>
<tr>
<td>WBC</td>
<td>≥ 15*10⁹/l</td>
</tr>
<tr>
<td>Lymphocytes count</td>
<td>&lt; 0.6*10⁹/l or &lt; 8% WBC</td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt; 4 g/dl</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt; 10.5 g/dl (&lt; 105 g/l or &lt; 6.5 mmol/l)</td>
</tr>
</tbody>
</table>

♦ age 16-60 years
♦ no prior therapy for Hodgkin's disease
♦ WHO performance status grades 0, 1, or 2
♦ no potentially childbearing patients without effective contraception
♦ patients should not be pregnant or lactating.
♦ no concomitant or previous malignancies other than basal cell skin tumors or in situ uterine cervix carcinoma.
♦ no severe cardio-pulmonary, neurological or metabolic disease, interfering with normal life expectancy or normal application of protocol treatment (patients with LEVF<50 and RF<30% are not eligible)
♦ no severe active infection
no psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule

no known HIV or HTLV1 positivity

adequate liver (bilirubin ≤ 2.5 x normal) and renal (creatinine ≤ 150 µmol/L or ≤ 2.0 mg/dL) function, unless abnormalities are due to HD

leukocytes >2.0*10^9/l and platelets >100*10^9/l

no history of uncontrolled HBV infection defined as presence of HBS antigen or absence of HBS antigen but presence of anti-HBc antibody without anti-HBS antibody

written informed consent according to ICH/GCP and/or applicable national laws. Parent’s consent for patients under 18 years of age according to applicable national laws.

4 Trial Design

This is a prospective randomized phase III trial, aiming at documenting a difference between the randomized arms (design based on a "difference" hypothesis).

Eligible patients will be randomized to receive either 4 cycles of BEACOPP at the escalated dose followed by 4 cycles of BEACOPP at the baseline dose (GHSG regimen) or 8 cycles of ABVD at the standard dose. Disease will be assessed at the end of the 4th cycle, at the end of the 6th cycle, and at the end of the 8th cycle of treatment. Patients will be randomized after objective documentation of all eligibility criteria, and before the start of chemotherapy. Randomization will be stratified according to the International Prognostic Score.

8 ABVD

Random

4 BEACOPP_E + 4 BEACOPP_B

ABVD: adriamicin, bleomycin, vinblastine, dacarbazine

BEACOPP: cyclophosphamide, adriamicin, vincristine, bleomycin, etoposide, procarbazine, prednisone

BEACOPP_E: escalated dose; BEACOPP_B: baseline dose

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 General guidelines

Chemotherapy is intended to be given in an outpatient setting. The full treatment in both arms consists of 8 cycles of chemotherapy. In case of toxicity (defined as any adverse event that can be possibly related to the treatment), the dosage and schedule of all these cycles should be adapted
following the schemas described in the chapter 5.2. Moreover, additional checkpoints must be fulfilled for pursuing treatment as planned:

♦ At the end of the 4th cycle (the end of the cycle is the last day of the cycle; i.e. the 22nd or 28th day, depending on the arm, after the first day of drug administration in this cycle): achievement at least of a PR (regression of more than 50% or PR>50%) & normalization of bone marrow biopsy in case of initial involvement

♦ At the end of the 6th cycle (the end of the cycle is the last day of the cycle; i.e. the 22nd or 28th day, depending on the arm, after the first day of drug administration in this cycle): achievement at least of a CRu (PR 75%)

If protocol therapy is discontinued for any reason while patient is in PR, progression, or unknown status at time of protocol treatment discontinuation, or when the physician judges that a new treatment is needed, this will be defined and recorded as an event (treatment failure).”

No radiotherapy can be given as part of the protocol treatment. The initiation of radiotherapy will be considered as protocol treatment failure for the principal end-point.

5.2 Treatments

5.2.1 Standard arm (ABVD)

5.2.1.1 Dosage and schedule

The standard treatment consists of 8 cycles of ABVD of 28 days each (normal duration). The dosage of drugs, the schedule and the way of their administration are given in the following table.

<table>
<thead>
<tr>
<th>drug</th>
<th>one day dose</th>
<th>way of administration</th>
<th>schedule (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Adriamycin</td>
<td>25 mg/m²</td>
<td>i.v.</td>
<td>d1 &amp; 15</td>
</tr>
<tr>
<td>B Bleomycin</td>
<td>10 mg/m²</td>
<td>i.v., i.m.</td>
<td>d1 &amp; 15</td>
</tr>
<tr>
<td>V Vinblastine</td>
<td>6 mg/m²</td>
<td>i.v.</td>
<td>d1 &amp; 15</td>
</tr>
<tr>
<td>D DTIC/Dacarbazine</td>
<td>375 mg/m²</td>
<td>i.v.</td>
<td>d1 &amp; 15</td>
</tr>
</tbody>
</table>

5.2.1.2 Expected toxicity

Acute toxicity:

♦ hematological toxicity (blood cell counts) should be expected. However, the vital complications occur extremely rarely.

♦ nausea & vomiting (N&V) due to dacarbazine may be significant

♦ total reversible alopecia occurs in most cases

♦ rare bleomycin intolerance have been reported (see below).

♦ ABVD –related toxic deaths have been reported, but not exceeding 2-3%.

Late toxicity:

♦ cardiac (adriamycin) & pulmonary (bleomycin) sequellae have been reported relatively frequently

♦ gonadal toxicity may be reversible in most instances

♦ very rare cases of MDS & leukemia have been reported
5.2.1.3 Treatment modifications

The treatment can be modified only because of toxicity.

In case of toxicity related to one particular drug, and leading to the omission or substitution of this drug, see the chapter 5.3.

The treatment on the first day of the first cycle is given at the full dose, regardless to the blood cells counts (patient inclusion criteria do guarantee that the patients included in the trial are able to receive the first cycle at the full dosage). At the day 15 of the 1st cycle the treatment is also given at full dosage, unless a CTC grade IV infection occurs before the day 15. In this case, on day 15 the treatment should be postponed up to 2 weeks. If, after the delay, there is no more CTC grade IV infection, the protocol treatment is given at the full dose. If the CTC grade IV infection persists beyond these 2 weeks, the treatment is stopped.

Depending on the toxicity on the day 1 and the day 15 (the day 1 is considered independently from the day 15), each following cycle is first postponed and then the dose is reduced if necessary (see 5.2.1.3.1).

5.2.1.3.1 Treatment postponement

For either day 1 or 15 of the subsequent cycles the treatment schedule must be adapted like following:

♦ If the blood cells counts are: leukocytes $<2.5 \times 10^9/l$ or platelets $<80 \times 10^9/l$, or any life-threatening toxicity CTC grade 4 (including intercurrent infection), the planned day of treatment (day1 or/and day15) is delayed by one week.

♦ if, after 1 week, the blood cells counts are: leukocytes $\geq 1.0 \times 10^9/l$ or platelets $\geq 50 \times 10^9/l$ and there is no life-threatening toxicity CTC grade 4, the treatment is given at the dosage corresponding to the blood cells counts (see 5.2.1.3.2).

♦ if, after 1 week, the blood cells counts are: leukocytes $<1.0 \times 10^9/l$ or platelets $<50 \times 10^9/l$, or there is a life-threatening toxicity CTC grade 4, another week delay is allowed.

♦ After this 2nd week, if the blood cells counts are: leukocytes $\geq 1.0 \times 10^9/l$ or platelets $\geq 50 \times 10^9/l$ and there is no life-threatening toxicity CTC grade 4, the treatment is given at the dosage corresponding to the blood cells counts (see 5.2.1.3.2).

♦ After this 2nd week, counts are: leukocytes $<1.0 \times 10^9/l$ or platelets $<50 \times 10^9/l$, or there is a life-threatening toxicity CTC grade 4, the protocol treatment will be stopped, and this will be considered as treatment failure.

5.2.1.3.2 Dose modifications

For either day 1 or 15 of the subsequent cycles the treatment dosage must be adapted like following:

♦ if blood cells counts are: leukocytes $\geq 2.5 \times 10^9/l$ or platelets $\geq 80 \times 10^9/l$ and there is no life-threatening toxicity CTC grade 4, the full dosage is given

♦ if the blood cells counts are within certain limits: leukocytes 1.0-2.5x10^9/l or platelets 50-80x10^9/l and there is no life-threatening toxicity CTC grade 4, all drugs (except bleomycin still 100%) in the following administration will be reduced to 50% of the starting dose.

♦ if the blood cells counts are below these limits despite postponement, the protocol treatment will be stopped, and this will be considered as treatment failure.

The use of G-CSF is allowed in case of leukocytopenia (see chapter 5.4).

The following scheme summarizes the modifications of the treatment.
**ABVD treatment modification scheme (see also chapter 5.3).**

**Day 1 of the 1st cycle: Full dose**
- Adriamycin 100%
- Bleomycin 100%
- Vinblastine 100%
- DTIC/Dacarbazine 100%

**Day 15 of the 1st cycle**
- Ongoing CTC grade IV infection
  - No: Full dose
  - Yes: up to 2 week delay
    - Disappears: Full dose
    - Persists: STOP

**Day 1 or 15 of the next cycle**
- Leukocytes <2.5x10^9/l or platelets <80x10^9/l or toxicity CTC grade 4*
  - 1 week delay
  - Leukocytes ≥2.5x10^9/l and platelets ≥80x10^9/l and no toxicity CTC grade 4*
    - Full dose 50% reduction
    - Adriamycin 50%
    - Bleomycin 100%
    - Vinblastine 50%
    - DTIC/Dacarbazine 50%

- Leukocytes ≥1.0x10^9/l <2.5x10^9/l or platelets ≥50x10^9/l <80x10^9/l and no toxicity CTC grade 4*
  - Full dose 50% reduction
  - Adriamycin 50%
  - Bleomycin 100%
  - Vinblastine 50%
  - DTIC/Dacarbazine 50%

- Leukocytes <1.0x10^9/l or platelets <50x10^9/l or persisting toxicity CTC grade 4*
  - Treatment should be stopped
  - Adriamycin 50%
  - Bleomycin 100%
  - Vinblastine 50%
  - DTIC/Dacarbazine 50%

*: any life-threatening CTC grade 4 toxicity, including intercurrent infection
5.2.2 Experimental arm (BEACOPP).

The BEACOPP guidelines are directly derived from the English version of the HD-12 protocol, very kindly provided by the GHSG.

This treatment consists of 4 cycles of BEACOPP escalated dose followed by 4 cycles of BEACOPP baseline dose.

5.2.2.1 Dosage and schedule

The dosage of drugs, the schedule and the way of their administration are given separately for the escalated BEACOPP and the baseline BEACOPP regimen in the tables below. The total duration of one cycle in both BEACOPP, escalated and baseline, is 22 days.

BEACOPP escalated dose (one cycle)

<table>
<thead>
<tr>
<th>abr.</th>
<th>Drug</th>
<th>one day dose</th>
<th>adm.</th>
<th>schedule (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Bleomycin</td>
<td>10 mg/m²</td>
<td>i.v., i.m.</td>
<td>d8</td>
</tr>
<tr>
<td>E</td>
<td>Etoposide *</td>
<td>200 mg/m²/day</td>
<td>i.v.</td>
<td>d1 to d3</td>
</tr>
<tr>
<td>A</td>
<td>Adriamycin</td>
<td>35 mg/m²</td>
<td>i.v.</td>
<td>d1</td>
</tr>
<tr>
<td>C</td>
<td>Cyclophosphamide</td>
<td>1250 mg/m²</td>
<td>i.v.</td>
<td>d1</td>
</tr>
<tr>
<td>O</td>
<td>Oncovin/Vincristine</td>
<td>1.4 mg/m²(max 2mg)</td>
<td>i.v.</td>
<td>d8</td>
</tr>
<tr>
<td>P</td>
<td>Procarbazine</td>
<td>100 mg/m²/day</td>
<td>p.o.</td>
<td>d1 to d7</td>
</tr>
<tr>
<td>P</td>
<td>Prednisone**</td>
<td>40 mg/m²/day</td>
<td>p.o.</td>
<td>d1 to d14</td>
</tr>
</tbody>
</table>

BEACOPP baseline dose (one cycle)

<table>
<thead>
<tr>
<th>abr.</th>
<th>Drug</th>
<th>one day dose</th>
<th>adm.</th>
<th>schedule (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>B</td>
<td>Bleomycin</td>
<td>10 mg/m²</td>
<td>i.v., i.m.</td>
<td>d8</td>
</tr>
<tr>
<td>E</td>
<td>Etoposide *</td>
<td>100 mg/m²/day</td>
<td>i.v.</td>
<td>d1 to d3</td>
</tr>
<tr>
<td>A</td>
<td>Adriamycin</td>
<td>25 mg/m²</td>
<td>i.v.</td>
<td>d1</td>
</tr>
<tr>
<td>C</td>
<td>Cyclophosphamide</td>
<td>650 mg/m²</td>
<td>i.v.</td>
<td>d1</td>
</tr>
<tr>
<td>O</td>
<td>Oncovin/Vincristine</td>
<td>1.4 mg/m²(max 2mg)</td>
<td>i.v.</td>
<td>d8</td>
</tr>
<tr>
<td>P</td>
<td>Procarbazine</td>
<td>100 mg/m²/day</td>
<td>p.o.</td>
<td>d1 to d7</td>
</tr>
<tr>
<td>P</td>
<td>Prednisone**</td>
<td>40 mg/m²/day</td>
<td>p.o.</td>
<td>d1 to d14</td>
</tr>
</tbody>
</table>

* 113mg Etoposide phosphate is equivalent to 100mg Etoposide
** Prednisone can be replaced by an equivalent dose of Dexamethasone (5 mg/m²/day). The treatment with Dexamethasone (instead of Prednisone) is still considered as the protocol treatment

5.2.2.2 Mandatory concomitant treatment

Both Uromitexan/Mesna and G-CSF are mandatory for the escalated BEACOPP cycles.

1. Uromitexan/Mesna i.v., together with cyclophosphamide and 4 and 8 hours after (20% of cyclophosphamide dose, last dose may be given p.o.). Patient should also drink 2.5 l of fluid on the day of cyclophosphamide treatment.

2. Prophylactic **G-CSF is mandatory for escalated regimen** and optional for the baseline regimen. The G-CSF should be given from the day 9 (the day after bleomycin administration), until leukocytes recovery (3 days with leukocytes greater than 1.0 x 10⁹/l after passing through nadir). The recommended dose is: 5 µg/kg/d when using filgrastim (if any other G-CSF is used the equivalent dose should be given).

The G-CSF should be discontinued at least 48h before the next treatment cycle.
GELA patients should refer to the Group Specific Appendix for more details on G-CSF.

### 5.2.2.3 Expected toxicity

#### Acute toxicity:
- Hematological toxicity (blood cells count) is significant and G-CSF is required with escalated BEACOPP to avoid vital complications. The CTC grade 4 leukopenia ($\leq 1.0 \times 10^9/l$) and CTC grade 4 thrombocytopenia ($\leq 25 \times 10^9/l$) have been observed with escalated BEACOPP. As nadir may be expected near days 11-12 (4 days duration for escalated BEACOPP), daily or 2-daily blood sampling should be done as soon as the CTC grade 4 hematological toxicity is observed and until improvement (see 5.2.2.4.2, 5.2.2.4.3).
- Rare procarbazine and bleomycin intolerance have been reported (see 5.3.)
- Nausea & vomiting (N&V) due to procarbazine may be significant
- Total reversible alopecia occurs in most cases.
- BEACOPP–related toxic deaths have been reported not to exceed those observed with standard ABVD, 2-3%.

#### Late effects:
- Cardiac (adriamycin) & pulmonary (bleomycin) sequelae have been reported relatively frequently
- Gonadal toxicity may be irreversible in a significant No. of cases
- MDS & leukemia (mostly etoposide-related) have been reported less rarely than with ABVD

### 5.2.2.4 Treatment modifications

The treatment can be modified only because of toxicity.

In case of toxicity related to one particular drug, and leading to the omission or substitution of this drug, see chapter 5.3.

#### 5.2.2.4.1 BEACOPP escalated

First cycle is given at the full dosage (patient inclusion criteria do guarantee that the patients included in the trial are able to receive the first cycle at the full dosage) regardless the blood values. Depending on toxicity, the following cycles are first postponed and then the dose is reduced if necessary (see 1.2.2.4.2. & 1.2.2.4.3.).

As nadir may be expected near days 11-12 (4 days duration for escalated BEACOPP), daily or 2-daily blood sampling should be done in all the cycles as soon as the CTC grade 4 hematological toxicity is observed and until improvement.

#### 5.2.2.4.2 Treatment postponement

If at the day of planned treatment start/continuation, the leukocyte counts are under $2.5 \times 10^9/l$ and platelets under $80 \times 10^9/l$, the treatment is postponed and the blood parameters are checked again on days 3, 7, 10, and 14 after first control. Therapy is to be continued as soon as the required values are reached.

If, after 14 days the leukocyte and platelets counts are below these values, the treatment is given following the dose modification scheme.
5.2.2.4.3 **Dose modifications**

Starting from the 2nd cycle the dosage of all subsequent cycles should be adapted if one or more of the following events is notified:

- **leukocytes:** $<1.0 \times 10^9/l$ for more than 4 days during the previous cycle
- **granulocytes:** $<0.5 \times 10^9/l$ for more than 4 days during the previous cycle
- **platelets:** $<25 \times 10^9/l$ during the previous cycle
- **infection:** CTC grade 4 during the previous cycle
- **any life-threatening toxicity:** CTC grade 4 during the previous cycle
- **14 days treatment postponement** of the present cycle

- When one or more of these events occurs before the day of the treatment start, the dosage will be adapted (one level lower).
- Once reduced, dosage will not be increased again (even if recovery and no more events occurred).
- If, during one of the subsequent cycles:
  - the dose was reduced by one step in the previous cycle and the dosage should be reduced again in the present cycle, an immediate reduction to **baseline** dosage follows
  - the dose was reduced by one step earlier, but not in the previous cycle (the reduction was just maintained) and the dosage should be reduced again, the dose will be reduced by one more level
- When **baseline** level is reached, further modifications of the BEACOPP treatment follow the **baseline dose** reduction guidelines, as specified in chapter 5.2.2.4.2. However, even if some of BEACOPP escalated cycles are given at the baseline dosage it will not reduce the total number of cycles in this treatment arm (8 cycles).
- The dose levels are presented in the table 1.

**Table 1: Dose reduction steps**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reduction step</th>
<th>full dose</th>
<th>step 1</th>
<th>step 2</th>
<th>baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin (day 8)</td>
<td></td>
<td>10 mg/ m²</td>
<td>10 mg/ m²</td>
<td>10 mg/ m²</td>
<td>10 mg/ m²</td>
</tr>
<tr>
<td>Etoposide (days 1 to 3)</td>
<td></td>
<td>200 mg/m²/ day</td>
<td>175 mg/m²/ day</td>
<td>150 mg/m²/ day</td>
<td>100 mg/m²/ day</td>
</tr>
<tr>
<td>Adriamycin (day 1)</td>
<td></td>
<td>35 mg/ m²</td>
<td>35 mg/ m²</td>
<td>35 mg/ m²</td>
<td>25 mg/ m²</td>
</tr>
<tr>
<td>Cyclophosphamide (day 1)</td>
<td></td>
<td>1250 mg/m²</td>
<td>1100 mg/m²</td>
<td>950 mg/m²</td>
<td>650 mg/m²</td>
</tr>
<tr>
<td>Oncovin/Vincristine (day 8)</td>
<td></td>
<td>1.4 mg/m² (max 2mg)</td>
<td>1.4 mg/m² (max 2mg)</td>
<td>1.4 mg/m² (max 2mg)</td>
<td>1.4 mg/m² (max 2mg)</td>
</tr>
<tr>
<td>Procarbazine (days 1 to 7)</td>
<td></td>
<td>100 mg/m²/ day</td>
<td>100 mg/m²/ day</td>
<td>100 mg/m²/ day</td>
<td>100 mg/m²/ day</td>
</tr>
<tr>
<td>Prednisone (days 1 to 3)</td>
<td></td>
<td>40 mg/ m²/ day</td>
<td>40 mg/ m²/ day</td>
<td>40 mg/ m²/ day</td>
<td>40 mg/ m²/ day</td>
</tr>
</tbody>
</table>

Following scheme summarize the BEACOPP **escalated dose** modifications.
**BEACOPP escalated dose reduction scheme (see also chapter 5.3)**

*1st cycle: Full dose (regardless blood cells counts)*

1st day of the 2nd cycle:

<table>
<thead>
<tr>
<th>Leukocytes $\geq 2.5 \times 10^9$/l and platelets $\geq 80 \times 10^9$/l</th>
<th>Leukocytes $&lt; 2.5 \times 10^9$/l or platelets $&lt; 80 \times 10^9$/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>up to 14 days delay (check on day 3, 7, 10, 14)</td>
<td>if after 14 days leukocytes $&lt; 2.5 \times 10^9$/l or platelets $&lt; 80 \times 10^9$/l</td>
</tr>
</tbody>
</table>

During the 1st cycle:

- leukocytes: $< 1.0 \times 10^9$/l for more than 4 days
- granulocytes: $< 0.5 \times 10^9$/l for more than 4 days
- platelets: $< 25 \times 10^9$/l
- infection: CTC grade 4
- any life-threatening toxicity: CTC grade 4

During the 2nd cycle:

- leukocytes: $< 1.0 \times 10^9$/l for more than 4 days
- granulocytes: $< 0.5 \times 10^9$/l for more than 4 days
- platelets: $< 25 \times 10^9$/l
- infection: CTC grade 4
- any life-threatening toxicity: CTC grade 4

During the 3rd cycle:

- leukocytes: $< 1.0 \times 10^9$/l for more than 4 days
- granulocytes: $< 0.5 \times 10^9$/l for more than 4 days
- platelets: $< 25 \times 10^9$/l
- infection: CTC grade 4
- any life-threatening toxicity: CTC grade 4

During the 4th cycle:

- leukocytes: $< 1.0 \times 10^9$/l for more than 4 days
- granulocytes: $< 0.5 \times 10^9$/l for more than 4 days
- platelets: $< 25 \times 10^9$/l
- infection: CTC grade 4
- any life-threatening toxicity: CTC grade 4

<table>
<thead>
<tr>
<th>Was the 2nd cycle reduced?</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same dose as in the 2nd cycle</td>
<td>2nd cycle dose reduced by one step</td>
<td>Baseline dose*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Was the 3rd cycle reduced?</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same dose as in the 3rd cycle</td>
<td>3rd cycle dose reduced by one step</td>
<td>Baseline dose</td>
</tr>
</tbody>
</table>

*If the 3rd cycle is given at the baseline dosage, the 4th cycle follow the BEACOPP scheme (next chapter). If, following that scheme the 4th cycle dosage is reduced furthermore, the 1st of the 4 BEACOPP cycles will be adapted consequently (see scheme on page 23).

**Dosage is never increased again**
5.2.2.4.4  **BEACOPP baseline**

The first BEACOPP baseline cycle is given at the schedule and dosage depending on the blood values. The treatment is first postponed and then the dose is reduced, if necessary.

If at the day of planned full dose BEACOPP baseline cycle, the leukocyte counts are: <2.5 x 10⁹/l and platelets are:<80 x 10⁹/l, the treatment is postponed and the blood parameters are checked again on days 3, 7, 10, and 14 after first control. Therapy is to be continued as soon as the required values are reached (see scheme on page 23).

If, after 14 days, the blood cells counts are still below the fixed limits, the etoposide, the adriamycin, the cyclophosphamide and the procarbazine should be reduced to 75% of full dosage.

If during one of the 75% dose BEACOPP baseline cycles there is any of the following events:

- **leukocytes:** <1.0 x 10⁹/l for more than 4 days during the previous cycle
- **granulocytes:** <0.5 x 10⁹/l for more than 4 days during the previous cycle
- **platelets:** <25 x 10⁹/l during the previous cycle
- **infection:** CTC grade 4 during the previous cycle
- **any life-threatening toxicity:** CTC grade 4 during the previous cycle

The next cycle should be postponed one week.

If, after one week, the leukocyte counts are: ≥2.5 x 10⁹/l and platelets are: ≥80 x 10⁹/l, the 75% treatment continue.

If, after one week, the blood cells counts are below these limits, the etoposide, the adriamycin, the cyclophosphamide and the procarbazine should be reduced to 50% of full dosage.

If, during the 50% treatment, there is again any of the following events:

- **leukocytes:** <0.1 x 10⁹/l for more than 4 days during the previous cycle
- **platelets:** <25 x 10⁹/l during the previous cycle
- **infection:** CTC grade 4 during the previous cycle
- **any life-threatening toxicity:** CTC grade 4 during the previous cycle

The protocol treatment will be stopped, and this will be considered as early discontinuation.

Once reduced, the dose cannot be increased again.

Following scheme summarize the BEACOPP baseline dose modifications.
**BEACOPP baseline dose reduction scheme** (see also chapter 5.3)

**At the Day 1**

(100% dose baseline BEACOPP cycles)

- **Leukocytes** ≥ 2.5x10^9/l and **platelets** ≥ 80x10^9/l
- **Leukocytes** < 2.5x10^9/l or **platelets** < 80x10^9/l

**Full dose**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>100%</td>
</tr>
<tr>
<td>Etoposide</td>
<td>100%</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>100%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>100%</td>
</tr>
<tr>
<td>Oncovin/Vincristine</td>
<td>100%</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>100%</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100%</td>
</tr>
</tbody>
</table>

**75% treatment**

- **Bleomycin** 100%
- **Etoposide** 75%
- **Adriamycin** 75%
- **Cyclophosphamide** 75%
- **Oncovin/Vincristine** 100%
- **Procarbazine** 75%
- **Prednisone** 100%

**During the 75% treatment cycle**

- **Leukocytes**: < 1.0 x 10^9/l for more than 4 days
- **Granulocytes**: < 0.5 x 10^9/l for more than 4 days
- **Platelets**: < 25 x 10^9/l
- **Infection**: CTC grade 4
- **Any life-threatening toxicity**: CTC grade 4

**Next cycle 1 week delay**

- **Leukocytes** ≥ 2.5x10^9/l and **platelets** ≥ 80x10^9/l
- **Leukocytes** < 2.5x10^9/l or **platelets** < 80x10^9/l

**50% treatment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
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</thead>
<tbody>
<tr>
<td>Bleomycin</td>
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</tr>
<tr>
<td>Etoposide</td>
<td>50%</td>
</tr>
<tr>
<td>Adriamycin</td>
<td>50%</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>50%</td>
</tr>
<tr>
<td>Oncovin/Vincristine</td>
<td>100%</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>50%</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100%</td>
</tr>
</tbody>
</table>

**During the 50% treatment cycle**

- **Leukocytes**: < 1.0 x 10^9/l for more than 4 days
- **Granulocytes**: < 0.5 x 10^9/l for more than 4 days
- **Platelets**: < 25 x 10^9/l
- **Infection**: CTC grade 4
- **Any life-threatening toxicity**: CTC grade 4

*The treatment should be stopped*
5.3 Substitution/omission of medication

For all three regimens:

If the patient develop heart failure responsive to treatment (cardiac left ventricular function CTC grade 3) the adriamycin should be stopped. In this case, the patient should be treated at the discretion of the investigator out of the protocol and any further treatment will no longer be considered as protocol treatment.

In case of bleomycin hypersensitivity (interstitial pneumonitis CTC grade ≥2) bleomycin should be stopped without substitute. In case the pulmonary lung function tests performed after the 4th or the 6th cycle show a reduction of either the total lung capacity (TLC) of > or = 20% or of the CO diffusion (DLCO) of > or = 30%, bleomycin should be stopped without substitute. However, treatment without bleomycin is still considered as the protocol treatment.

For BEACOPP arm:

In case of the gross hematuria with clots requiring catherisation or instrumentation or transfusion (hematuria ≥ CTC grade 3) the cyclophosphamide should be stopped. In this case, the patient should be treated at the discretion of the investigator out of the protocol and any further treatment will no longer be considered as protocol treatment.

If the patient cannot tolerate vincristine (neuropathy ≥ CTC grade 3, constipation ≥ CTC grade 3), it has to be replaced by vinblastine 4mg/m². If besides this replacement, the neuropathy and/or constipation persist, the vinblastine has to be stopped without any replacement. However, treatment without vincristine (with or without vinblastine) is still considered as the protocol treatment.

If the patient has procarbazine allergy, it has to be replaced by chlorambucil 6mg/m²/d (max 10 mg total dose per day). If besides this replacement, the allergy persist, the chlorambucil has to be stopped without any replacement. However, treatment without procarbazine (with or without chlorambucil) is still considered as the protocol treatment.

5.4 Supportive care

♦ G-CSF is mandatory for escalated BEACOPP cycles but may also be used also in the baseline BEACOPP cycles and the ABVD arm (Silvestri et al, Tumori 80:453-458,1994; Rueda et al. Leukemia and Lymphoma 2000).

♦ prophylaxis of cyclophosphamide induced hemorrhage cystitis with Uromitexan/Mesna on day 1 (BEACOPP escalated cycles) is mandatory

♦ mandatory antibiotic prophylaxis (with co-trimoxazol)

♦ following supportive care is not mandatory, should be considered:

♦ EPO allowed according to the investigators’ discretion

♦ anti-emesis with 5-HT3 receptor antagonists

♦ medication with allopurinol and H2 receptor blocker should be considered where appropriate.

♦ placement of an implantable infusion port (vascular access device) is highly recommended

5.5 Reasons to stop the protocol treatment

♦ 8 cycles completed (normal end of protocol treatment)

♦ <PR (tumor regression <50%) after 4 cycles and <CRu (PR <75%) after 6 cycles

♦ progression, relapse or death any time
♦ excessive toxicity that does not allow to give the protocol treatment (see chapter 5.2.)
♦ refusal of patient to further cooperate (at any time and because of any reason)
♦ investigator's decision that the protocol treatment is not anymore in the best interest of the patient

5.6 Modalities of drug administration

**ADM** Adriamycin has vesicant properties. It must be infused slowly (5 min.) directly into intravenous tubing with physiologic saline or 5% dextrose solution kept running to wash the vein.

**BLM** Bleomycin. i.m. injection or i.v. injection. Rare & severe anaphylactic reactions have been reported.

**VLB** Vinblastine. Due to possible phlebitis, VLB must be injected directly into intravenous tubing with physiologic saline solution or 5% dextrose solution kept running to wash the vein.

**DTIC** Dacarbazine has vesicant and emetic properties and should be infused in 5 to 10 minutes in a fast running infusion. Protect the infusion from light.

**VP16** Etoposide. Must be administered slowly i.v. (over at least 30 minutes) in order to avoid hypotension.

**CPM** Cyclophosphamide. i.v. injection directly into intravenous tubing with physiologic saline solution or 5% dextrose solution kept running to wash the vein or as a 250 ml infusion.

**VCR** Vincristine. Due to possible phlebitis, VCR must be injected directly into intravenous tubing with physiologic saline or 5% dextrose solution kept running to wash the vein.

**PCZ** Procarbazine. p.o. Intravenous administration is also possible.

**PDN** Prednisone, p.o. Intravenous administration is also possible.

6 Clinical evaluation, laboratory tests and follow-up

This chapter resumes all the investigations to be done during the protocol, including the quality of life assessment timepoints (for more details refer to the corresponding chapter).

This chapter includes all the examinations to be done in the best interest of patients included in this protocol. The actual data collected through CRFs to achieve the end-points of the protocol will not include all of these items.

6.1 Before treatment start

**History:**
Anamnesis, menstrual & contraception status for women.

**Pathology:**
Tumor biopsy for histologic typing: WHO / REAL classification (Ref. 45). Tumor immunophenotype and cytogenetics are not mandatory for the local pathologist, but should be recorded if done for the central pathologist.
Bone marrow biopsy (unilateral Jamshidi posterior iliac crest, with 1.5 cm minimum length of bone cast. Diagnosis only by an experienced hematopathologist (material remains available for central review).

A liver biopsy may be desirable in case of cholestasis, enlarged or heterogeneous liver, enlarged or heterogeneous spleen, especially if B symptoms.

**Imaging:**
- Chest X-ray.
- CT-scan of thorax and abdomen & pelvis.

Nodal & extranodal tumor masses will be measured (CT-scan: largest diameter x its perpendicular diameter). The Magnetic Resonance Imaging (MRI), gallium scan, Positron Emission Tomography (PET) ultrasound, bone scintigraphy and lymphangiogram might be useful, but can not replace the CT-scan to measure the lesions and evaluate response.

Measure of large mediastinal mass is to be done according to the Cotswolds recommendation (Ref. 15): ratio M/T= largest transverse diameter of the mass (14 cm) / internal transverse diameter of the thorax at the T5 - T6 level (26 cm) ⇒ ratio M / T = 0.43 after Cotswolds (not mandatory, Ref. 15)

**Blood tests:**
- Complete blood count (CBC) with differential, MCV and serum chemistry panel (blood urea nitrogen [BUN], serum creatinine, total protein, albumin, alkaline phosphatase, ALAT or ASAT, gamma-GT(optional), LDH, total bilirubin, glucose)
- EBV, CMV, HBV, HCV, HIV serologies (optional)
- ESR (optional).
- Blood grouping & irregular agglutinins (optional).

**Physical examination:**
- WHO performance status, B symptoms, weight and height.
- Complete clinical physical examination, including dental status and measurement and repartition (diagram & date) of all palpable lymph nodes (largest diameter x its perpendicular diameter); respiratory symptoms (cough, dyspnea, shortness of breath).

**Cardiac/Pulmonary function tests:**
- Heart evaluation: Left Ventricular Ejection Fraction (isotopic or ultrasound), EKG (optional).
- Lung function evaluation with CO diffusion.

**Quality of life assessment**

**QLQ C30 questionnaire**

**Fertility:**
- Cryopreservation of sperm & spermogram and oocytes should be offered.
6.2 Investigations during treatment

6.2.1 Before & during each cycle

Blood tests:
Complete blood count (CBC) with differential prior each chemotherapy course (day 1 for the BEACOPP regiments and day 1 & day 15 for ABVD).
Daily or 2-daily CBC should be done during escalated BEACOPP as soon as any hematological toxicity CTC grade 4 appears and until improvement (around day 11-12).

Physical examination:
WHO performance status, weight, complete clinical physical examination.

Complete clinical physical examination. Measurement and repartition (diagram & date) of all palpable lymph nodes (largest diameter x its perpendicular diameter).

Toxicity assessment:
The CTC grading
Lung function evaluation with CO diffusion will be performed at the end of the 4th and 6th cycles (just before the 5th and the 7th cycles). History of respiratory symptoms (cough, dyspnea, shortness of breath) will be investigated at each cycle.

6.2.2 Intermediate response evaluation of patients

Patients will be evaluated at the end of the 4th and 6th cycles (just before the 5th and the 7th cycles). The end of the cycle is at the day 22 or 28 after the first injection depending on the arm.
Response will be classified as a CR, CRu (PR 75%), PR, stable or progressive disease, according to standardized response criteria (adapted from Cheson Ref. 15).

Only patients who achieved at least a PR with no bone-marrow infiltration left, at the end of the 4th cycle will be allowed to continue the protocol treatment.
They will be re-evaluated before the start of the 7th cycle. Similarly, only patients who achieved at least a CRu (PR 75%) at the end of the 6th cycle will be allowed to continue the protocol treatment.
Therefore, some additional investigations will be performed.

Pathology:
Bone marrow, if originally involved. Optional: liver biopsy, if originally involved.

Imaging:
Chest X-ray, if abnormal initially
CT-scan of thorax and abdomen & pelvis, if abnormal initially.
Nodal & extranodal tumor masses will be measured (CT-scan: largest diameter x its perpendicular diameter). The Magnetic Resonance Imaging (MRI), gallium scan, Positron Emission Tomography (PET) ultrasound, bone scintigraphy and lymphangiogram might be useful, but can not replace the CT-scan to measure the lesions.
Physical examination:
WHO performance status, B-symptoms
Complete clinical physical examination. Measurement and repartition (diagram & date) of all palpable lymph nodes (largest diameter x its perpendicular diameter).

6.3 Investigations when stopping the protocol treatment
Patients will be evaluated at the time of progression or at the end of the last cycle of treatment (the normal end of the cycle is at the day 22 or 28 after the first injection in the cycle depending on the arm). This evaluation should be done regardless the total number of cycles received by patient (i.e. even if the patient did not succeeded to complete all 8 cycles and stopped earlier).

Pathology:
Bone marrow biopsy if initially positive

Imaging:
Chest X-ray, if abnormal initially
CT-scan of thorax and abdomen & pelvis, if abnormal initially.
Nodal & extranodal tumor masses will be measured (CT-scan: largest diameter x its perpendicular diameter). The Magnetic Resonance Imaging (MRI), gallium scan, Positron Emission Tomography (PET) ultrasound, bone scintigraphy and lymphangiogram might be useful, but can not replace the CT-scan to measure the lesions.

Blood tests:
Complete blood count (CBC) with differential, MCV and serum chemistry panel: blood urea nitrogen [BUN], serum creatinine, total protein, albumin, alkaline phosphatase, ALAT or ASAT, gamma-GT (optional), LDH, total bilirubin, glucose, ESR (optional: persistent elevation of the ESR, while not diagnostic for active HD, calls for very close follow-up).

Physical examination:
WHO performance status, B-symptoms
Complete clinical physical examination. Measurement and repartition (diagram & date) of all palpable lymph nodes (largest diameter x its perpendicular diameter).

Additionally:
In case of response less then CRu (PR 75%), it is advised to assess the nature of the residual mass with additional diagnostic studies (MRI, Gallium, PET according to the center policy), including pathological examination (biopsy of peripheral, mediastinal or infradiaphragmatic node or mass).

Quality of life assessment
QLQ C30 questionnaire

6.4 Follow-up investigations
Patients will be evaluated at each follow-up visit. Follow-up visits are scheduled at least every three months during the first 3 years and every six months during the 4th and 5th year and yearly thereafter.
At each examination the following investigations will be done:

**Imaging:**
Chest X-ray, if abnormal initially, CT-scan thorax, and abdomen & pelvis at 6, 12 & 24 months post-treatment and in case of progression.
Optional: ultrasound (abdominal, pelvic or on peripheral nodal areas on the occasion of the 3-monthly visits)

**Blood tests:**
Hemoglobin, platelets, leukocytes including differential, MCV, alkaline phosphatase, LDH, ESR (optional). Serum chemistry.

**Physical examination:**
WHO performance status, B symptoms, complete clinical examination, secondary tumor
Complete clinical physical examination and history of respiratory symptoms (cough, dyspnea, shortness of breath).
Response evaluation (including measurement of all palpable lymph nodes (largest diameter x its perpendicular diameter).

**Late toxicity evaluation**
Cardiac, pulmonary and gonadal evaluation at 2, 5 & 10 year post-treatment (see recommended initial work-up)

**Quality of Life assessment:**
Will be evaluated yearly regarding the different dimensions (scales) of the QLQ C30 questionnaire.

### 6.5 Relapse / Progression

At any time the relapse / progression of the initial disease occurs, should be reported:

- date of relapse / progression
- type of relapse / progression
  - site of relapse / progression
  - nodal areas (previously involved or uninvolved)
  - extranodal areas (previously involved or uninvolved)
  - histologic type of relapse (a biopsy is also recommended to exclude other lymphomas).

### 6.6 Death

Causes of death will be registered and categorised, as follows:

- Hodgkin’s disease
- Treatment related
- Intercurrent death
- Second tumor, including MDS/leukemia and other type of lymphoma
### 6.7 Summary of Protocol Investigations

<table>
<thead>
<tr>
<th>Examinations</th>
<th>Before treatment start</th>
<th>During the treatment before each cycle</th>
<th>after the 4th/6th cycle</th>
<th>End of treatment</th>
<th>Follow-up &gt;3 years (1/3 month)</th>
<th>Follow-up &gt;3 years (1/6 month)</th>
<th>Follow-up &gt;5 years (yearly)</th>
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</tbody>
</table>

*: if abnormal initially; **: at 6, 12 and 24 month; y: yearly; CRu (PR 75): if PR > 75%; L: 2, 5 and 10 years post treatment.
7 Criteria of evaluation

7.1 Event free survival

The primary end-point is Event Free Survival (EFS). This end-point is defined as the time from randomization until the date of first event. If no event is observed, this end-point will be censored at the date of last follow-up.

In this protocol, an event (treatment failure) will be defined as

♦ discontinuation of the protocol therapy, for any reason (including the early discontinuation after 4 or 6 cycles because of not achievement of adequate response) or

♦ absence of CR after 8 cycles or

♦ relapse or progression at any time or

♦ death from any cause

7.2 Response criteria

Complete response rate and disease free survival are secondary end-points in this trial.

The criteria for response evaluation according to the recommendations of the Cotswolds Meeting updated in the NCI International Workshop (from Cheson 1999:Ref. 15) will be used and adapted to the Hodgkin's Lymphoma. Therefore, the modified criteria will be in bold italic.

During the initial measurement, a maximum of 6 target lesions will be identified. These lesions (node, nodal mass or measurable extranodal lesion) should be selected according to the following features:

♦ they should be clearly measurable in at least two perpendicular dimensions

♦ they should be from as disparate regions of the body as possible

♦ they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

Response to treatment will be evaluated after the 4th and the 6th cycle and at the end of treatment (one month after the day of the first injection of the last cycle).

The Response Criteria for Hodgkin's Lymphoma are summarized in the following table:

<table>
<thead>
<tr>
<th>Response</th>
<th>Physical examination</th>
<th>Lymph nodes, lymph node masses, measurable extranodal masses</th>
<th>Bone marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Normal, no radiological abnormality</td>
<td>&gt;1.5 cm</td>
<td>≤1.5 cm</td>
</tr>
<tr>
<td><strong>CRu</strong> (PR≥75%)</td>
<td>Normal</td>
<td>&gt;1.5 cm</td>
<td>&gt;75% SPD decrease</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>Normal, decrease in liver/spleen ; 6 target lesions : ≥50% SPD decrease</td>
<td>no increase</td>
<td></td>
</tr>
<tr>
<td><strong>NC</strong></td>
<td>▲ ▲</td>
<td>▲ ▲</td>
<td>▲ ▲</td>
</tr>
<tr>
<td><strong>Relapse</strong></td>
<td>New sites, enlarged liver/spleen involved</td>
<td>≥50% SPD increase of &gt;1node (Re)-appearance</td>
<td></td>
</tr>
<tr>
<td><strong>Progression</strong></td>
<td>New lesion(s) involved</td>
<td>≥50% SPD increase from nadir (Re)-appearance</td>
<td></td>
</tr>
</tbody>
</table>
7.2.1 Complete remission (CR)

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities definitely assignable to HD.

2. All lesions (node, nodal mass or measurable extranodal lesion) must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to 1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

3. The spleen, if considered to be enlarged before therapy on the basis of a CT scan, must have regressed in size and must not be palpable on physical examination. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size. Any macroscopic nodules in any organ detectable on imaging techniques should no longer be present. Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

4. If the bone marrow was involved by lymphoma before treatment, the infiltrate must be cleared on repeat bone marrow biopsy of the same site. The sample on which this determination is made must be adequate (20 mm biopsy core).

7.2.2 Complete Remission uncertain (CRu [i.e. PR 75%])

1. Criteria 1, 3 & 4: same as listed above for CR: no clinical or biological or bone marrow evidence of HD, but some radiological abnormality persists at the site of previous disease (when adapted to HD, the criteria are more strict: the bone marrow should be negative if involved initially).

2. Criterion 2: a residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

7.2.3 Partial remission

1. At least 50% decrease in SPD of the six largest dominant lesions.

2. No increase in the size of the other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by at least 50% in the SPD.

4. With the exception of splenic and hepatic nodules, involvement of other organs is considered assessable and not measurable disease. This consideration concerns the majority of the extranodal sites, which are not measurable. However, a clearly measurable extranodal lesion can be considered as target lesion.

5. Bone marrow should be negative, if involved initially (when adapted to HD, the criteria are more strict than originally)

6. No new sites of disease.

There should also be an improvement in non-evaluable, but clinically evident malignant disease, and resolution of "B" symptoms.

7.2.4 No change or Stable disease

No change or Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).
7.2.5 **Progressive disease**

Progressive disease (PD) requires the following:
1. 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
2. Appearance of any new lesion during or at the end of therapy. A biopsy is recommended to exclude opportunistic infections or other lymphomas.

7.2.6 **Relapsed disease**

Relapsed disease (in patients who achieved CR, CRu (PR 75%)) requires the following:
1. Appearance of any new lesion or increase by 50% in the size of previously involved sites.
2. 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

7.3 **Disease free survival**

Disease free survival will be evaluated in all patients who have achieved a complete response (CR or CRu). According to recommendations of the Cotswolds Meeting (see above), it will be computed from the day of first documentation of CR or CRu to the day of relapse. Patients who died in CR or CRu will be censored at the date of death.

7.4 **Overall survival**

Overall survival will be measured from the date of randomization to the date of death, whatever the cause. Patients alive at the time of analysis will be censored at the date of last follow-up.

7.5 **Quality of life**

Related end-points are described in the chapter on "Quality of life" (chapter 10).

7.6 **Cost-effectiveness**

Related end-points are described in the chapter on "Economic evaluation" (chapter 11).

8 **Statistical considerations**

8.1 **Statistical design**

8.1.1 **Sample size**

The primary end-point in this trial is event free survival, as earlier described (see 7.1).

The present study aims at detecting a difference between the two therapeutic arms. In the control group, the 3-years event free survival rate is estimated to be 70%. The present trial is powered to detect an event free survival benefit that would result in a 10% difference between therapeutic arms at 3 years, i.e. from 70% to 80%; this corresponds to a hazard ratio of 0.62.

A two sided logrank test will be used, with the following parameters: alpha=0.05, beta=0.8.
With one interim analysis (see 8.3), a total of 152 events should be observed to perform the final analysis.

A total number of 550 patients will be included in this trial. With a yearly accrual rate of 100 patients, the duration of recruitment will be approximately 5.5 years. Under these hypotheses, 152 events should occur within 8 months of trial closure. The final analysis will be conducted as soon as 152 events are recorded, and the full protocol treatment is documented for all patients.

### 8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter 16 on registration / randomization procedure). A minimization technique will be used for random treatment allocation stratifying by institution and according to the International Prognostic Score (IPS) at entry (3 vs 4+).

### 8.2 Analysis

The principal analysis of all end-points (except toxicity) will be performed according to the "Intent To Treat" (ITT) policy. All randomized patients (even if later found to be ineligible) will be included in these analyses.

All "time to event" end-points will be evaluated by the Kaplan-Meier method, and comparisons will use a two-sided logrank test. Proportion of complete responses will be computed in each arm with a 95% confidence interval.

The conclusions of the trial will be based on the analysis of the principal end-point. Analysis of other efficacy end-points are intended to better understand the mechanism of action of the therapeutic regimen, and should therefore be considered as sensitivity analysis. They should not be used to conclude on the superiority of one of the regimens above the other. Tests will be performed at the alpha=0.05 level.

Analysis on side effects will be based on all patients who have started protocol therapy, and will be descriptive only. The worst grade of each CTC toxicity item recorded during the whole treatment period will be tabulated. For the most frequently observed events, the proportion of grade 4 (hematological) toxicities and of grade 3 or 4 (non hematological) toxicities will be computed with a 95% confidence interval.

Occurrence of secondary malignancy will be estimated by the cumulative incidence method, using death as a competing risk; the Gray test will be used for comparisons.

### 8.3 Interim Analyses of efficacy

One interim analysis will be performed after observation of a total of 50 events. With a recruitment rate of 100 patients/year, this will likely occur after 3 to 4 years of recruitment.

The interim and final analysis will be conducted using the EAST software. An error spending function with a boundary parameter equal to 0.2 will be used. This is a compromise between the O'Brien Fleming and the Pocock approach.

### 8.4 Stopping rule for toxicity

The toxic death rate will be evaluated every 6 months in patients in whom at least 4 CT cycles have been documented (or who died of toxicity before the 4th cycle could be given). If the lower limit of the 95% confidence interval is superior to 3% in one of the arm, the results will be submitted to the IDMC, that may recommend the closure of the trial.
8.5 End of study
End of study occurs when all of the following criteria have been satisfied:
1. Thirty days after all patients have stopped protocol treatment
2. The trial is mature for the analysis of the primary endpoint as defined in the protocol
3. The database has been fully cleaned and frozen for this analysis

9 Independent data monitoring committee
This trial will be monitored by the EORTC Independent Data Monitoring Committee (IDMC), in accordance with the EORTC IDMC policy.

As soon as the first 50 events have been observed, a confidential interim analysis will be performed and submitted to the IDMC, that will make appropriate recommendations to the Steering Committee for the further conduct of the trial.

The IDMC will also be consulted in case the lower limit of the 95% confidence interval of toxic death rate is above 3%. Based on these results, the IDMC may decide to close the trial for excessive toxicity.

10 Quality of life assessment
Reducing mortality and morbidity is still the most important factor in clinical research. Nevertheless, issues such as reducing side effects, symptom relief and patients satisfaction have also become relevant parameters in the evaluation of medical strategies. Cancer treatments may produce adverse effects and diminish the QoL even when survival is extended. Progress in the acceptance of new cancer therapies is sometimes critically dependent on their QoL consequences. Health related QoL is a multidimensional concept which represents the physiological, psychological and social influences of the disease and the therapeutic process from the patients perspective. It comprises four principal components: physical, psychological and social well-being, and daily-life functioning.

10.1 Rationale
In this study QoL is a secondary endpoint. The main objective of QoL assessment within this clinical trial is to determine the impact of an initially more intense therapy (BEACOPP escalated + BEACOPP baseline) on overall health/QoL. The $H_0$ hypothesis will be tested that there is no difference between patients in both arms after treatment. A secondary objective is to evaluate the effect of BEACOPP escalated + BEACOPP baseline on the various symptoms and functioning scales as treatment related side-effects may have a negative influence on the health related domains of QoL of these patients. The aim of QoL evaluation in this study is to get a better understanding of the effects of BEACOPP escalated + BEACOPP baseline in terms of frequency and degree of treatment related side-effects and longer term effects from the patients’ perspective.

10.2 QL instrument
The QoL questionnaire of the EORTC Quality of Life Study Group in its current published version QoLQ C30 v3.0 will be used to assess QoL. This is composed of multi-item and single scales.
These include five functional scales (physical, role, emotional, social, and cognitive), three symptom (fatigue, nausea and vomiting and pain) and a global health status/QOL scale and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). All scales and single items meet the standards for reliability. The reliability and validity of the questionnaire is highly consistent across different language-cultural groups [Aaronson et al., Ref. 1].

10.3 Study design

Patients are eligible for the quality of life assessment in this study if they fulfil the eligibility criteria (Section 3) and, more importantly, complete the baseline quality of life questionnaire before randomization. Patients will be informed in the patient informed consent form that they will have their quality of life assessment regularly while involved in this trial. QoL will be a secondary outcome and will be evaluated in a longitudinal design for in all patients entered in this study.

10.3.1 QoL data collection- Timing and where and how.

QoL will be assessed on all patients entered into the study as an integrated part of the trial.

QoL questionnaires must be filled out at the hospital when the patients come for a scheduled visit. The questionnaire will be handed out to the patients by the investigator or a study nurse prior to seeing the doctor for clinical evaluations. Patients will be asked to fill out the questionnaires as completely and accurately as possible. The average time to complete the entire questionnaire is approximately 10-15 minutes. Mastercopies of the QoL questionnaires (EORTC QLQ-C30) will be sent to the institution together with the CRFs. The clinical forms will include a question whether the QoL forms have been filled in -and if not, the reason why. Data collection procedures should be followed using the EORTC guidelines in appendix D.

Time windows for eligible assessment before treatment will be +/- 1 week and for eligible follow-up assessment will be +/- 2 weeks the scheduled follow-up assessment.

The questionnaire should be completed within a week prior to randomization, then at the end of treatment.

During the follow-up period, the patient will receive a QoL questionnaire on a yearly basis. The follow-up period will last for 10 years or until death if it occurred earlier.

10.3.2 Compliance

Missing data may hamper assessment of QL in clinical trials. This may be because centres do not collect the questionnaires at the appropriate time (unit non-response), and because patients may miss questions within the questionnaires (item non-response). The latter problem occurs less than 2% on average and should not be a problem. The former problem will be minimised by ensuring that participating centres are properly informed and motivated about QL assessment.

During the study, compliance with completing QoL questionnaires will be investigated at each time point. The compliance of the QoL assessments will also be reviewed twice a year and will be a part of the descriptive report by Data Center for the Group's plenary sessions.

The compliance rate between the 2 arms will be compared at each time point using a chi-square test. In order to adjust for the multiplicity of the tests, a Bonferroni adjustment will be made by which each test will be performed at the 0.01 significance level. Should serious volumes of missing questionnaires occur then the protocol writing committee would review the QL assessment in the trial.
10.4 Statistical considerations

A longitudinal analysis will be performed to detect differences in the QoL outcome, regarding the different dimensions of quality of life (QoL) in the two treatment groups.

The primary QL endpoint that is considered relevant to this trial is global QL. The QL data will inform the hypothesis that specific QL issues such as e.g. haematological toxicity, will be effected by different therapeutic strategies.

In the absence of more specific hypothesis, the global quality of life scale of the QOQ-C30 will be used as the primary QL outcome of interest. Based on the work of Osoba et al. (Ref. 47), a difference of 10 points on a 100 point scale between the two treatment arms will be considered as clinically significant. The standard deviation of the global QL scale is approximately 20 points. With a minimal effect size of 0.5 (i.e. one-half standard deviation), with alpha set at 0.5 and beta at 0.20 (power 0.80), a minimum of 64 patients per treatment arm is required. The other scales will only be analysed on an exploratory basis.

Data will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual. All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where:

A high score for a symptom scale or item represents a high level of symptoms or problems.

A high score for a functional scale represents a high or healthy level of functioning.

A high score for the global health status/QoL represents high QoL.

When performing a QoL analyses complications may arise due to large quantities of missing data. This issue has a bearing on whether a valid comparison of the treatment arms is being made.

In QoL research there are two main types of missing data: (1) item non-response, (2) unit non-response (the whole questionnaire is missing for a patient). As item non-response occurs less than 2% on average in the QLQ-C30 it is not such a major problem and thus the methods described in the EORTC QLQ-C30 scoring manual for handling item non-response will be used. For missing questionnaires, it is necessary to identify both the extent of missing questionnaires and the main process of missing data. Three different types of missing data processes may exist: missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR, informative dropout mechanism). These have distinct consequences for data analysis.

If the missing data process is considered to be non-ignorable (MNAR) then the quality of life will be compared between groups using longitudinal data modelling techniques (i.e. Proc mixed in SAS with either selection models or pattern-mixture models) in combination with a logistic regression for the dropout process.

If the missing data mechanism can be considered ignorable (MAR), then standard longitudinal data analysis will be used (prox mixed in SAS).

If the data are MCAR then complete case analysis can be used without biasing the results.

Statistical tests will be performed using a two-sided significance level of 5%.

For all quality of life domains and items, cross-sectional descriptions of the average scores will be presented by treatment arm at each time point of assessment together with confidence intervals and a graphical display of the patterns of change over time will be provided.
11 Economic evaluation

Each group participating to this protocol will stipulate in the GSA weather or not they will participate to the economic evaluation.

11.1 Clinical Background

See clinical background, chapter 1 of protocol.

11.1.1 Rationale

Both short-term and long-term cost-analysis are worthwhile in this study. The overall survival differences were significantly better in the 2 combined BEACOPP arms versus COPP/ABVD. During its administration, although slightly shorter (24 versus 32 weeks), the more intensive BEACOPP regimen with 2x4 cycles is expected to be much more costly than the standard ABVD 8 cycles regimen (supportive care like prophylactic use of antibiotics and growth factors and also increased likelihood of adverse events and/or hospitalization days for febrile neutropenia) its cost-effectiveness is worth being assessed (short-term analysis). However, progressions, relapses and disease-related deaths are expected to be more frequent in the ABVD arm. As treatment for relapses and pre-exitus maneuvers are known to be extremely costly, no guess can be made about the final cost balance. Therefore, in addition to the induction period, the collection of minimal information during the follow-up periods plus some summary information about the therapy given in case of progression/relapse will be performed by all participating centers (long-term analysis). The second part of the economic evaluation, the costing (i.e. to put a price on these medical resources) will be done only with the help of selected centers in each group participating in the economic evaluation.

11.1.2 Health Economics Literature Review

Several researchers have presented results of high-dose chemotherapy (HDC) with/without PBSCT in various malignancies, although only one was found that specifically studied BEACOPP and ABVD in Hodgkin’s disease.

Kath et al.(1998) [Ref. 39] investigated the cost of 37 patients with HDC and PBSCT in breast cancer and various other malignancies, including Hodgkin’s disease between July 1994 and June 1997 in Germany. All patients with HDC experienced grade IV neutropenia and thrombocytopenia of average duration of respectively 11 and 14 days. The cost structures of the whole patient group was made up of 38% for blood products, 35% for GCSF’s and 13% for chemotherapy.


Some more attention has been paid recently to the cost of relapsed or resistant lymphoma patients, especially with the advent of blood stem cell transplantation coupled to HDC.

Sanna et al.( 1998) [Ref. 56] studied the use associated with a HDC of 5 drugs (cyclophosphamide, methotrexate, etoposide, mitoxantrone, melphalan) with PBSC support in a small sample of 20 patients Bellinzona, Switzerland.

They concluded the HDC regimen was feasible but at the cost of frequent hospitalizations for drug administration and treatment for complications. In their sample the average number of days per patient spent in hospital was 44 days.

Mazza et al. (1999) [Ref. 44] documented the cost of PBSCT in 21 patients with resistant malignant lymphoma in northern Italy in 1995. Total cost, including support after treatment was equal to...
$18,063 on average. Myeloablative therapy and reinfusion accounted for only 15% of the total cost (mean 2, $786). The highest cost was that of support after treatment with a mean of $7,649 or 42% of the total average cost.

Recently Beard et al. (2000) [Ref. 6] used results from two randomized clinical trials of HDC in lymphoma with “ad hoc” cost data to derive an estimates of the additional cost of HDC. These authors estimated the additional cost of HDC to 17,375£ (with first line therapy equal to 13,900£) for an average gain of 0.8 life-years. This would translate itself in an incremental cost per life-year gained of 21,718£. Extending the observed life years gained in the trials over a 20 year period they estimated an average of 78 life-months gained, resulting in a dramatic decrease of the incremental cost-effectiveness.

A recent abstract presented at the 2000 meeting of the American Society for Hematology (ASH) by R Walsh et al. (2000)[Ref. 64] compared the cost-effectiveness of COPP/ABVD versus BEACOPP escalated based on the HD-9 German Hodgkin’s Lymphoma Group trial on 262 and 403 patients respectively. Median observation time of trial patients was 40 months (3.3 years). Cost calculations were based on direct medical costs observed at the university hospital of Köln, Germany and covered cost of treatment, outpatient visits to the hospital, inpatient admissions and cost of salvage therapy in relapsed/resistant patients.

The difference in survival extrapolated over 5 years was equal to 3.2 months on average. The cost difference between the two arms was equal to $34,037 ($35,084 BEACOPP– $25,983 COPP/ABVD). Cost differences between the two arms were mainly due to the use of GCSF, cost of chemotherapy drugs and blood products and cost of inpatient hospitalizations for treatment and toxicity.

It is therefore important to document these resources carefully in any prospective trial involving HDC in Hodgkin’s patients.

The assessment of such effects is warranted in the new setting of both a prospective and an Intergroup study that involves European, South African and Canadian centers looking at a similar comparison between an intense non-myeloablative regimen (escalated BEACOPP / baseline BEACOPP) and a standard dose regimen (ABVD).

11.2 Objective

11.2.1 Aim of Economic Study

To compare the cost-effectiveness of the escalated BEACOPP regimen with the standard ABVD regimen in unfavorable stage III&IV Hodgkin’s disease in previously untreated adult patients below age of 60 with IPS status ≥ 3.

11.2.2 Perspective

The perspective will be that of the public health authorities and public social security systems

11.3 Methods

11.3.1 Type of Economic Evaluation.

Given an expected difference in effectiveness a cost-effectiveness (CEA) analysis is warranted.
11.3.2 **Choice of Comparator.**
The comparator will be the standard ABVD treatment as defined in the comparison arm of the clinical trial (see protocol chapter 5) as ABVD is the accepted standard chemotherapy by most investigators.

11.3.3 **Patient population**
The patient population for the economic evaluation is the same as defined by the inclusion/exclusion criteria of the clinical trial. It is therefore not representative of older patients and of patients that undergo adjuvant irradiation as this was not retained in the design of the trial, although this last strategy might be used in practice.

11.3.4 **Center selection**
The general economic analysis will be performed on all available data from all centers of the collaborating groups participating to the Health economics evaluation. This will involve the analysis of the volume of medical resources used in each arm and the pricing of these resources by one single country price list (generally the country which contributed most of the patients).

The pricing/costing part of the Health economics evaluation will depend on the availability of “health economic” staff in each country and the number of patients recruited in each country.

Final inclusion of countries with their specific local price in the pricing/costing part of the economic evaluation will depend on the accrual (only the countries, which enrolled at least 30 patients, will be included) and on the availability of at least 1 local (health) economist or person skilled in economic evaluation of health care technologies to help with the local pricing/costing.

One or two reference centers per country participating in the economic price/costing evaluation will be selected and relied upon to provide more economic detailed data not collected through the CRF’s (for example additional detailed medical resources consumption data, hospital unit costs, reimbursement tariffs, etc…). The EORTC Health Economics Unit will manage this additional retrospective data collection.

11.3.5 **Measurement of Resource Use.**

11.3.5.1 **The data to be used in the Health Economics analysis.**

11.3.5.1.1 **Baseline information**
The only baseline information that will be used in the economic evaluation is on the cryopreservation of sperm & spermogram or oocytes as the proportion might differ between the two arms.

11.3.5.1.2 **During the treatment**
Medical resources to be collected and monitored during this phase of active treatment will cover:

- Hospital days: inpatient (patient staying longer than 24h) and outpatients with a distinction being made for these last ones between day hospitalization – (patient in bed but not staying overnight)- and ambulatory visits (patient sitting in a chair) as different unit cost are related to different modalities of chemotherapy administration and type of ward (ICU, Hematology, Oncology, etc…)

- The hospital days needed for chemotherapy administration will be tracked
Unplanned hospitalizations (due to any event and especially to the SAE or severe toxicity grade 3-4) will also be documented.

Events (based on diagnosis at time of discharge) leading to hospitalization will recoded using the ICD-9-CM classification either through a link with the Medra System classification if possible or else separately.

- Chemotherapy: dosage, number of cycles, dose delivered, including dose reductions and dose delays
- Supporting therapy: growth factors (GCSF, EPO), antiemetics (5HT classes), and prophylactic antivirals and antibiotics. The only information collected for the supporting therapy will be whether it was given or not.
- Blood transfusions (Platelets, packed RBC, …): nature of product and quantity (units) transfused
- Costly diagnostic procedures: MRI, CT-Scan, Gallium Scan, endoscopy

11.3.5.1.3 Follow-up after planned chemotherapy

- Hospitalizations and costly diagnostic procedures will be documented.
- Summary data of second and third line therapy given in case of progression or recurrence will be collected. Information regarding date of treatment, type of treatment (radiation therapy, lines of chemotherapy, number of cycles, whether high dose chemotherapy was followed by autologous/allogeneic transplant with or without myeloablative conditioning/stem cell transplantation, number of transplants, monoclonal antibodies use) will be collected for each treatment episode.
- Date of first observation and type and stage of secondary tumor will be collected through the clinical forms. Medical resources used for treatment of secondary tumors will not be collected prospectively in the trial but will be collected retrospectively outside the trial if needed or assessed through an expert panel.
- Late toxicities after primary or secondary chemotherapy/radiotherapy will only be collected and costed if they result in unforeseen hospitalizations. Each hospitalization for toxicity, SAE or any other reason will be documented, describing the number of days in the hospital, and type of ward. (ICU or other)
- In case of death, whether palliative care was given and the duration of palliative care (in weeks) and the setting (hospital, specialized center, at home) will be documented

11.3.5.2 Data collection schedule for the economic evaluation.

Most information required for the Health Economics evaluation (see 11.3.5.1) is already covered by the investigations during the protocol treatment (see 6.7). However, some additional information will be collected during the trial for exclusive Health Economics purposes. The summary of this additional information is represented in the following table.

Information to be collected for the Health Economics evaluation.
Additionally, during the analysis, the Health Economics Unit might collect some retrospective additional data in a few selected centers.

### 11.3.6 Measurement of Unit Costs.

#### 11.3.6.1 Chemotherapy

Cost of chemotherapy will be derived from national drug list prices or otherwise from hospital pharmacy purchasing prices if available.

#### 11.3.6.2 Adverse events

Costs of adverse events will be based on the collected medical resources trial data in first instance, where available a national Diagnosis-Related Group based cost (i.e. PMSI in France) will also be linked to adverse events having led to hospitalization as observed from the trial data (SAE reports and hospitalization forms).

#### 11.3.6.3 Radiation therapy

Cost of secondary radiation therapy will either be based on locally available data from the economic reference centers or in fee-for-service reimbursement systems from the official price lists, based upon doses given as retrieved from the trial data.

#### 11.3.6.4 Secondary tumors

Standard cost of care for the treatment of secondary tumors will be retrieved from the literature or if not available based on standard practice defined by local clinical experts.

#### 11.3.6.5 Terminal care

The cost of terminal care depends on the setting (at home with regular support by ambulatory teams, in a hospital-based palliative care unit etc.) Standard per diem costs for each setting will be retrieved from published official reimbursement national sources or from local accounting data.

#### 11.3.6.6 Medical resources not costed

Work-ups, staging procedures, ambulatory care outside the hospital, non healthcare costs and patient out-of-pocket costs.
11.3.6.7 Country specific sources of information

Country-specific sources of information and costing will be described in the Group Specific Appendix of each group.

11.3.7 Measurement of Effectiveness for Economic Evaluation.

Overall Survival (OS) (calculated from the time of randomization until death) and Disease-Free Survival (DFS, calculated from the time of randomization to the first evidence of progression or death, whichever comes first) as available from the trial data will be used as endpoint for the economic analysis. Patients alive for whom no progression is observed at the time of analysis will be considered censored at the time of last follow-up examination available.

An exploratory analysis will be performed on the QLQC-30 overall summary score, depending on data availability and quality, to be used as a proxy weight measure for calculating Quality-adjusted Life-years (QALY’s).

11.3.8 Time Horizon

Time horizon of medical resources and economic data collection is equal to 3 years after the end of the treatment. Censoring of survival and costs will be acknowledged from the trial data collected.

11.3.9 Discounting

A 3% discounting factor for costs and life-years gained will be used in the cost-effectiveness calculations.

11.4 Statistical Analysis

11.4.1 Sample Selection

Main medical events and specific resource consumption will be collected from all participating centers, more detailed data (outside-trial data) will be collected retrospectively from the participating “reference-centers” in the economic analysis as will local unit costs. Additional clinical or cost data (i.e. average per diem costs, adverse events costs, etc…) from additional participating centers with large patient accrual might also be collected by retrospectively.

Final selection of centers retained for the economic analysis (apart from the reference-centers) will be decided in view of countries retained for the economic analysis and their patient accrual size.

11.4.2 Statistical Methods

All economic analyses will be conducted from an Intention-to-treat perspective.

11.4.2.1 Effectiveness Measures

Differences in the area under the curve (AUC) in Life-Years gained, if possible adjusted for quality-of-life, between the two arms will be assessed using a restricted means (RM) approach with comparison of the differences in survival using a Logrank and Wilcoxon on the restricted mean survival period.
11.4.2.2 Volume of medical resources used

Differences in the number of units of medical resources used and the proportion of patients using a particular resource will be assessed using appropriate standard categorical or continuous tests (Chi-square, Mantel–Haenzel, t-test).

11.4.2.3 Costs

Differences in Mean Total Cost per patient in both arms will be compared by a parametric t-test and by bootstrap on the untransformed individual cost data.

Cumulative costs per arm will be calculated using the Lin (1997) [Ref. 40] and Carides (2000)[Ref. 14] methods for censored cost analysis.

All costs will be expressed in EURO.

11.4.2.4 Cost-effectiveness ratios

The Incremental Cost-Effectiveness Ratio (ICER) between both arms will be constructed and confidence intervals will be calculated using Fieller’s and bootstrapping methods and represented as acceptability and/or Net Health Benefit-Cost curves. The ICER will be calculated from the pooled data. If heterogeneity in resource use is detected then a country-specific subgroup analysis will be performed, depending on presence of a sufficient number of observations and cost data per country (see below)

11.4.2.4.1 Country and Center heterogeneity

Center and country effects on total cost per patient (restricted to resource costs collected from within the trial) will be identified by using a unique reference unit price for resource valuation and if necessary, using a multivariate hierarchical model or General Linear Mixed Model methodology (Goldstein, 1999).[Ref. 32]

If necessary, for multiple country comparisons and adjustment, the method of Wilke et al. (1998) [Ref. 66] will be used.

11.4.3 Sensitivity Analysis

Because most cost and efficacy data will be trial based, sensitivity analysis is only needed for data retrieved from secondary external sources when their distribution is known (f.ex. DRG-based costs of hospital admissions). If variance estimates are available, the influence of the possible variation cost retrieved from secondary sources on the C/E ratios will be assessed either through deterministic or stochastic methods.

11.5 Reporting of Results

11.5.1 Presentation of Economic Results

Economic results will be presented as mean and incremental Cost/Effectiveness ratios.

Confidence intervals for the incremental C/E ratio will be calculated and presented in a C/E plane, as well as the corresponding Cost-Acceptability Curve (CAC).

11.5.2 Publication Policy

See protocol chapter 23 on publication policy for economic studies.
11.6 **Collaboration with local Health Economics Research Groups.**

Collaboration will be sought with one Health Economics Research Group in each of the individual countries or Groups involved in the economic analysis to assist with local unit cost tracking, overall cost assessment and participation in the economic study.

In principle, no economic country specific evaluation will be performed without such support from the country/Group being available.

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12 **Pharmacokinetics**

No pharmacokinetic evaluation will be performed in this study.

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13 **Translational research**

No translational research project is included in this study.

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14 **Publication policy**

The final publication of the trial results will be written by the Study Chairman and co-Chairman on the basis of the final analysis performed at the EORTC Data Center. The study chairman will submit a draft manuscript to the Data Center for review no later than six months after receiving the Data Center report. After revision by the Data Center and other co-authors the manuscript will be sent to a major scientific journal.

Authors of the manuscript will include at least the Study Chairman and co-Chairman, the investigators who have included \( \geq 10\% \) of the eligible patients in the trial (by order of inclusion), the Data Center personnel in charge of the trial, the pathologist, and the QoL Study Coordinator (Quality of Life Study Group liaison officer). In a note participating centers with the responsible physicians, committee members and board of the groups must be mentioned.

If the group wishes to publish or present study data before this final publication, those will never include comparisons between randomized treatment arms before the number of events required by the protocol for the primary end-point of interest have been observed.

All publications, abstracts or presentations including data from the present trial will be submitted for review to the EORTC Data Center prior to submission.

The title of all manuscripts will include the name of all participating groups, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, as well as supporting bodies (NCI, cancer leagues, sponsors…).

The Steering committee must approve all publications, abstracts and presentations based on patients included in this study. This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms or an analysis of any of the study end-points unless the Study Coordinator has already published the final results of the trial.

Publication of the economic analysis will follow the “Uniform Requirements for Manuscripts Submitted to Biomedical Journals” of the International Committee of Medical Journal Editors.
(ICMJ) (full text available at http://www.icmje.org/). It will not be submitted before presentation of the final clinical results of the trial.

Authorship for the economic analysis will be decided accordingly with description of the contributions of each author. In principle the main economic analysis will have the responsible health economist as primary author in accordance with general EORTC policy (Policy 9 available at the EORTC web site (www.eortc.be). Other publications with an economic component will at least have to be reviewed by the responsible health economist to ensure compliance with international recognized standards and methodological guidelines for publication of economic evaluations.
Chapters 15 through 22 pertain specifically to the participation of EORTC investigators (with the exception of French investigators). For legal reasons, GELA will be the legal sponsor of the EORTC French investigators. Therefore, the EORTC French investigators should refer to the Group Specific Appendix of GELA. Participants from other organizations should consult the appendix that is specific to their group to determine if the contents of these chapters are superceded by procedures specific to their group.
15 Investigator authorization procedure

This chapter concerns all the EORTC investigators with the exception of French investigators (legal sponsor: GELA). The investigators of other groups should refer to the Group Specific Appendix (GSA)

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the Data Center:

♦ The updated signed and dated Curriculum Vitae of the Principle Investigator
♦ The (updated) list of the normal ranges, in their own institution, of all laboratory data required by the protocol, preferably signed and dated by the head of the laboratory.
♦ A commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,
  ♦ A signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared on the commitment form.
♦ A copy of the favorable opinion of their local or national (whichever is applicable) ethics committee mentioning the documents that have been reviewed (incl. version number and date of documents) and indicating the list of the ethics committee members.
♦ A copy of the translated, and adapted (according to all national requirements), Patient Information / Informed Consent sheet, clearly mentioning the version number and the date.
♦ The signature log-list of the staff members with a sample of each authorized signature and the indication of the level or delegations.
♦ The coordinates of the pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
♦ The accreditation letter for the laboratory. (if available for your center and/or applicable by your national law)

*The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol and / or the applicable national law*

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

♦ All the above mentioned documents are available at the Data Center
♦ All applicable national legal and regulatory requirements are being fulfilled

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.
16 Patient randomization procedure

Patient randomization will only be accepted from authorized investigators (see "Authorization procedure").

A patient can be randomized after verification of eligibility directly on the EORTC Data Center computer, 24 hours a day, 7 days a week, through the INTERNET network. To access the interactive randomization program, the investigator needs a username and a password (that can be interactively requested: http://www.eortc.be/random).

Alternatively randomization can be done by telephone to the EORTC Data Center from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday. As from January 01, 2003 the phone randomization will not be available on the official bank holiday of Belgium. A list of these dates will be available on our web site and updated yearly.

This must be done before the start of the protocol treatment.

Telephone: +32 2 77416 00
Internet: http://www.eortc.be/random

An exhaustive list of questions to be answered during the randomization procedure is included in the registration check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is randomized.

Standard questions
♦ institution number ?
♦ protocol number ?
♦ step number: 1
♦ name of the responsible investigator ?
♦ patient's initials (maximum 4 letters) ?
♦ patient's chart number (if available) ?
♦ patient's birth date (day/month/year) ?

Group affiliation
♦ primary group affiliation ?
♦ secondary group affiliation ?

Protocol specific questions
♦ eligibility criteria ?
  all eligibility criteria will be checked;
  actual values of the eligibility parameters will be requested when applicable
♦ stratification factors ?
♦ date of written informed consent ?

At the end of the procedure, the treatment will be randomly allocated to the patients, as well as a patient sequential identification number. This number and the allocated treatment have to be recorded on the randomization check-list, along with the date of randomization. The completed check-list must be signed by the responsible investigator and returned to the data center with the
initial data of the patient. The sequential identification number attributed to the patient at the end of the randomization procedure identifies the patient and must be reported on all case report forms.

17 Forms and procedures for collecting data

17.1 Case report forms and schedule for completion

Data will be reported on the EORTC forms and sent to:

Hodgkin's Lymphoma Data Manager
EORTC Data Center
avenue Emmanuel Mounier, 83, bte 11
B-1200 Brussels, Belgium

A. Before the treatment starts:
♦ the patient must be registered/randomized at the Data Center by INTERNET or by phone
♦ the registration check-list should be returned to the Data Center

The optimal way to work is to complete the registration check-list first and to register/randomize the patient as soon as it is completed. The date of registration and patient sequential identification number are then completed on the check-list, and this form can be sent to the Data Center.

B. The list of forms to be completed for this study and their submission schedule is appended to the set of case report forms

C. Upon occurrence of a Serious Adverse Event
♦ All Serious Adverse Events (SAE) occurring during the treatment period and within 30 days after the end of the last protocol treatment must be faxed to the EORTC Safety Desk.
♦ All Serious Adverse Events related to the protocol treatment, and occurring after this 30-day period must also be reported to the EORTC Safety Desk.
♦ All Serious Adverse Events must be reported by fax to the EORTC Safety Desk on a Serious Adverse Event Form (Form 89) within 24 hours of the initial observation.
♦ A completed SAE-form must be returned to the Data Center within 10 calendar days of the initial observation of the Serious Adverse Event.

ALL Forms must be dated and signed by the responsible investigator or one of his/her authorized staff members
17.2 Data flow

The case report forms must be completed, dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available.

The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to the Data Center by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to the Data Center and that they are completely and correctly filled out.

The original copy must be immediately returned to the EORTC Data Center and the investigator must keep a copy.

The EORTC Data Center will perform extensive consistency checks on the CRFs and issue Query Forms in case of inconsistent data. Those Query Forms must be immediately answered and signed by the investigator (or an authorized staff member). The original must be returned to the EORTC Data Center and a copy must be appended to the investigator's copy of the CRFs.

If an investigator (or an authorized staff member) needs to modify a CRF after the original copy has been returned to the EORTC Data Center, he/she should notify the Data Center in writing (and sign the notification) and append a copy of the notification to his own copy of the CRFs.

The investigator's copy of the CRFs may not be modified unless modifications are reported on a Query Form (or a written and signed notification) and the Query Form (or notification) reference is indicated on the CRF.

18 Reporting adverse events for chemotherapy trials

18.1 Definitions

An Adverse Event (AE) is defined as any untoward medical occurrence or experience in a patient or clinical investigation subject which occurs following the administration of the trial medication regardless of the dose or causal relationship. This can include any unfavorable and unintended signs (such as rash or enlarged liver), or symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment. (ICH-GCP)

An Adverse Drug Reaction (ADR) (marketed products) are responses to a drug which are noxious and unintended and which occur at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function. (ICH-GCP)

An Adverse Drug Reaction (ADR) (non-marketed products) is defined as any response to a medical product, that is noxious and/or unexpected, related to any dose. (ICH-GCP)

Response to a medicinal product (used in the above definition) means that a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

An Unexpected Adverse Drug Reaction is any adverse reaction for which the nature or severity is not consistent with the applicable product information (e.g., Investigators’ Brochure). (ICH-GCP)
A Serious Adverse Event (SAE) is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment. A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a Serious Adverse Drug Reaction (SADR).

Adverse events and adverse drug reactions which are considered as serious are those which result in:

♦ death
♦ a life threatening event (i.e. the patient was at immediate risk of death at the time the reaction was observed)
♦ hospitalization or prolongation of hospitalization
♦ persistent or significant disability/incapacity
♦ a congenital anomaly/birth defect
♦ any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

(ICH-GCP)

REMARK: In this study death due to progression of disease will not be considered as an SAE and must therefore not be reported as an SAE.

18.2 Reporting procedure

18.2.1 Non-serious adverse events and/or non-serious adverse drug reactions

Adverse Events (AE) and/or Adverse Drug Reactions (ADR) must be recorded as indicated in the protocol.

18.2.2 Serious adverse events or serious adverse drug reactions

All Serious Adverse Events (SAE), related or not to the protocol treatment, occurring during the treatment period and within 30 days after the last protocol treatment administration, must be reported to the EORTC Safety Desk. (Ref. http://ctep.cancer.gov/forms/CTCv20_4-30-992.pdf).

Any late Serious Adverse Drug Reaction (SADR), occurring after this 30-day period also must be reported to the EORTC Safety Desk.

This must be done by fax within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the protocol treatment (i.e. unrelated, likely related, and not assessable) and the decision will be recorded on the Serious Adverse Event form (form 89), if necessary with the reasoning of the principal investigator.
The assessment of causality is made by the investigator using the following definitions:

<table>
<thead>
<tr>
<th>Relationship to the protocol treatment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNRELATED</td>
<td>There is no evidence of any causal relationship to the protocol treatment</td>
</tr>
<tr>
<td>LIKELY RELATED</td>
<td>There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.</td>
</tr>
<tr>
<td>NOT ASSESSABLE</td>
<td>There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.</td>
</tr>
</tbody>
</table>

Details should be documented on the specified Serious Adverse Event Form (Form 89).

**PLEASE FAX THE REPORT TO:**

EORTC Safety Desk:

Fax No. +32 2 772 8027

The EORTC Safety Desk will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons (See Administrative chapter).

All unexpected SADR reports and all reports involving expected SADR that are life threatening or caused death, will additionally be forwarded to all participating investigators.

Upon receipt of a safety report, from the EORTC Safety Desk, it is the responsibility of the investigators to promptly report this to the Ethical Review Board (ERB) according to the local regulation.

To enable the EORTC Safety Desk/sponsor to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse drug reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Safety Desk will make a written request to the investigator.

**PLEASE SEND THE ORIGINAL REPORT TO:**

EORTC Safety Desk:

Avenue E. Mounier, 83, bte 11

B- 1200 Brussels

Belgium

It should be recognized that Serious Adverse Drug Reactions (SADR) which have not been previously documented in the Investigators’ Brochure, or which occur in a more severe form than anticipated (i.e. they are ‘unexpected’ by nature or severity), are subject to rapid reporting to the Regulatory Authorities by the sponsor/promoter.
19 Quality assurance

19.1 Control of data consistency

Data forms will be entered in the database of the EORTC Data Center by a double data entry procedure. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the Data Manager to be entered on the master database. Inconsistent forms will be kept "pending" until resolution of the inconsistencies.

19.2 External review of histology

In order to assure the high quality and consistent pathology diagnosis, a centralized pathology review is included in this trial.

Within two weeks from the date of registration, the local pathologist must send to the Panel Committee the following material:

♦ fifteen (15) unstained slides or paraffin block(s)
♦ the original pathology form (only the local pathology part should be completed)

Panel Committee address:

Jacques Marnay, Trial 20012,
Pathology Department
Centre François Baclesse, Route de Lion / Mer
F-14076 - Caen cedex 5, France.

The Panel Committee, including Dr J. Bosq, Dr. D. de Jong, Dr. K. MacLennan, Dr. J. Diebold., will review all received slides. Once this pathology review has been performed, the fully completed pathology form will be sent to the EORTC Data Center in Brussels.

The final diagnosis of the Central Pathologists will be considered as definitive for the trial.
The diagnosis made by the local pathologist of the participating center will be accepted for the registration.

20 Ethical considerations

20.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/pdfifpma/e6.pdf).

The protocol will be approved by the Local, Regional or National Ethics Committees.

20.2 Subject identification

The name of the patient will not be asked for nor recorded at the Data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient’s initials (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

20.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. An example of a patient informed consent statement is given as an appendix to this protocol.

It is the responsibility of the individual investigator to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the enclosed informed consent document are the sections that must appear in the translation.

The translated informed consent form is part of the documents to be submitted to the ethics committee for approval. The competent ethics committee for each institution must validate local informed consent documents before the center can join the study. It is the responsibility of the Local Ethical Committee to guarantee that the translation is conforming to the ICH-GCP guidelines.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This must be done in accordance with the national and local regulatory requirements.
For European Union member states, the informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that “the written informed consent form should be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

21 Administrative responsibilities

21.1 The study coordinator

The Study Coordinator (in cooperation with the Data Center) will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

Study coordinator:

Dr. Patrice CARDE
INSTITUT GUSTAVE ROUSSY
Dept of Medicine
39, rue Camille Desmoulins
F - 94805 VILLEJUIF CEDEX
France
Tel +33 (0)142114321
Fax +33 (0)142115270
E-mail carde@igr.fr

21.2 The EORTC Data Center

The EORTC Data Center will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Data Center.

EORTC DATA CENTER

83, avenue Emmanuel Mounier, Bte 11
B-1200 Brussels, Belgium
Fax: +32 2 7723545

Registration of patients:

Tel +32 2 7741600

or

http://www.eortc.be/random

Statistician:

Martine Van Glabbeke
Tel: +32 2 7741625
e-mail: mvg@eortc.be
Data Manager:

Bart Meulemans
Tel.: +32 2 7741079
e-mail: bme@eortc.be

Coordinating physician:

Dr. Ivana Teodorovic
Tel.: +32 2 7741692
e-mail: ite@eortc.be

Safety Desk:

Nathalie Dubois
Tel: + 32 2 174 1676
Fax: + 32 2 772 8027
e-mail: safetydesk@eortc.be

The EORTC Safety Desk will forward all SAE within 24 hours of receipt to the EORTC Study Coordinator and the EORTC Data Manager.

All unexpected SADR and all expected SADR that are life threatening or caused death, will additionally be forwarded to all EORTC participating investigators and all central Data Managers of all Cooperating Groups.

The EORTC Safety Desk will take in charge the reporting to the National Authorities for all EORTC reportable cases in cooperation with the Regulatory Desk Manager whenever applicable.

The EORTC Safety Desk will send a six-monthly summary of all SAE to the central Data Managers of all Cooperating (in parallel with the group meeting report).

21.3 The EORTC Lymphoma group

All questions concerning membership in the group should be addressed to the chairman and/or secretary of the group.

Chairman:
Dr. Houchingue Eghbali
Address: INSTITUT BERGONIE
229, cours de l’Argonne
F - 33076 BORDEAUX CEDEX
France
Phone: + 33 556333243
Fax: + 33 556333383
e-mail: eghbali@bergonie.org


22 Trial sponsorship and financing

The Sponsor of patients entered on behalf of EORTC (with the exception of patients from French institutions: legal sponsor GELA) in this study is the EORTC.

The Director General of the EORTC is:

Professor Françoise Meunier
EORTC Central Office
Avenue Mounier 83, Bte 11
B-1200 Brussels, Belgium
Tel: +32 2 7741641
Fax: +32 2 7712004
e-mail: fme@eortc.be

23 Trial insurance

The EORTC insurance program covers all patients entered on behalf of EORTC in EORTC studies except patients from USA, Canada and Australia.

23.1 Insurance within the European Union

When specific requirements are stated in the national laws of the E.U. countries, the insurance program will take these requirements into account.

For countries where there are no specific requirements, the EORTC provides an insurance coverage which is valid for two years after a patient has completed the treatment strategy being studied by the research protocol. This insurance program covers the EORTC as the sponsor, the investigators and all local hospital staff.

23.2 Insurance outside the European Union

The EORTC insurance program only covers claims against the EORTC as the sponsor in its role of co-ordinator of the research and not the investigators and local hospital staff.
Appendix A: References

Ref. 1 Aaronson-NK; Ahmedzai-S; Bergman-B; Bullinger-M; Cull-A; Duez-NJ; Filiberti-A; Flechtner-H; Fleishman-SB; et-al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J-Natl-Cancer-Inst. 1993 Mar 3; 85(5): 365-76


Ref. 5 Base nationale de coûts. Ministère de la Santé, 1999, Paris, France. (Internet : www.le-pmsi.fr)


Ref. 15 Cheson JCO 1999


Ref. 38 Karrison TG Use of Irwin’s restricted mean as an index for comparing survival in different treatment groups – interpretation and power considerations., Controlled Clinical Trials, 1997, Apr; 18(2): 151-167.


Ref. 45 N. Harris et al. The WHO classification. The Hematology Journal 1:53-66,2000


Ref. 50 Raemaekers J., Burgers M., Henry-Amar M et al. Patients with stage III/IV Hodgkin's disease in partial remission after MOPP/ABV chemotherapy have excellent prognosis after additional involved-field radiotherapy: Interim results from the ongoing EORTC-LCG and GPMC phase III trial. Ann. Oncol. 8 (suppl1.): S111-S114, 1997


Ref. 53 Robinson R. Costs and cost-minimization analysis. BM J 1993;307:726-8


**Appendix B: WHO performance status scale**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Performance scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Able to carry out all normal activity without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out light work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
Appendix C: International Common Toxicity Criteria

In the present study, toxicities will be recorded according to the

International Common Toxicity Criteria (CTC), version 2.0.

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: http://ctep.cancer.gov/reporting/ctc.html.

The EORTC Data Center web site http://www.eortc.be/ provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Investigators who do not have access to Internet can contact the Data Center to receive a hard copy of this document by mail.
Appendix D: EORTC Quality of Life evaluation: guidelines for administration of questionnaires (Revised January 2001)
EORTC Quality of Life evaluation: guidelines for administration of questionnaires (revised January 2001)

The instructions given below are intended to provide some general guidelines for collecting quality of life (QoL) data in EORTC studies. These instructions apply for all types of questionnaires.

1. **Who is the responsible person (RP) for QoL data collection?**

The overall-responsible person for QoL data collection is the study-co-ordinator of the trial. However, for practical reasons it is strongly recommended that one person is responsible for the organization of QoL data collection in each Institution. This can be a physician, data manager, (research) nurse or a psychologist. Such a person should have the full protocol at his/her disposal as well as the questionnaire. This person would also be the intermediate contact point in case of any necessary clarification asked by the Data Center.

2. **Who should fill out the questionnaire?**

In principle it is the patient him/herself who has to fill out QoL forms and preferably without help from others. In case a patient is too sick to fill out the questionnaire or if the patient is not able to fill out the questionnaire for reasons such as forgetting his/her glasses, another person could read the questions without making any comments and report the answers on the forms. If a patient received this type of help, please note this on the form.

3. **What instructions should be given to the patient?**

At entry in a study, the RP should give the patient an explanation of the objective of the study and instructions for filling out questionnaires.

The patient should be informed that participation in the QoL protocol is voluntary and that the information provided is confidential (identification is only for administrative purposes and includes patient’s initials, date of birth and today’s date).

The following issues should be explained to the patient:

- The schedule of assessments.
- The questionnaire is a self administered questionnaire that should be filled out preferably by the patient him (her) self.
- The patient should circle the choice that best corresponds to his/her situation.
- There is no right or wrong answer to any of these questions.
- All questions should be answered.

The RP should make sure that the patient understands the instructions.

At each subsequent assessment as defined by the protocol, the patient should receive the questionnaire from the RP or by other appropriate staff if the RP is not available.
4. Where should the patient fill out the questionnaire?

The patient should complete the questionnaire in the clinic, ideally in a quiet, private room. If this is not possible, the waiting room is an acceptable alternative. In general it does not take more than 5 to 10 minutes to fill out a questionnaire, but patients should be given the time they need to answer all questions.

5. When should the patient fill out the questionnaire?

When a QoL assessment is planned, the questionnaire should be given to the patient preferably before the meeting with the physician, ensuring that the patient has enough time to complete the questionnaire. If the patient receives a therapy, the questionnaire should be filled out before administration of the treatment. The questionnaire should not be taken home and/or mailed.

6. Review of the completed questionnaire.

After the patient has filled out the questionnaire, the person handling the questionnaire should:

♦ Check the answers for omissions, for incorrectly completed questions and for inconsistent answers;

If this is the case:

♦ Please ask the patient for the reason for omissions or incorrect answers. If the patient prefers not to answer a question this should be noted on the form;

♦ Additional explanation may be provided, but the questions should not be rephrased;

♦ Any additional comments could be added by the person handling the questionnaire (if possible in English) followed by their name and signature.

7. Missing forms

If for some reason the patient is unable or does not wish to complete a quality of life questionnaire the reason and date of visit should be documented on the questionnaire and returned to the person responsible for completing the CRF’s (case record forms).

8. Mailing to the Data Center

The questionnaire should be sent to the Data Center with the CRF’s. As it is not possible to retrospectively collect missing quality of life data, please make sure the patient completes the questionnaire at the time-point when he/she is supposed to fill it out.

Thank you very much for your cooperation. If you have any remarks on this leaflet or if you need further information, please contact:

Quality of Life Unit - EORTC Data Center:
Phone: 32 2 774 1678/1661
Fax: 32 2 779 45 68
EORTC Quality of Life evaluation: instructions for Monitors

♦ Check if all QL questionnaires have been filled out on schedule
♦ If not, the Monitor should inform the person in charge of data collection and explain again the schedule of the QL questionnaires.
♦ Make sure the QL questionnaires are correctly completed
♦ If not, tell the responsible person to explain again to the patient how to fill out the QL questionnaires at the next visit.

EORTC Quality of Life evaluation: instructions for Data Managers

1. When a response is missing, it should be coded as “9” for missing data (cfr Scoring Manual)

2. When two adjacent categories have been circled by the patient, the category which represents the worst QoL will be taken.

3. When two categories which are not adjacent have been circled, then the response is not evaluable and it should be coded as “8”.

Appendix E: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician’s knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for
those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of
funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician’s judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.
Appendix F: Informed consent document
Standard format for an EORTC informed consent document

This is a clinical trial.
Clinical trials include only patients who choose to take part.
Please take your time to make your decision.

Title of the research protocol: Intergroup Hodgkin BEACOPP / ABVD study (EORTC protocol 20012). A phase III randomized study on BEACOPP (escalated x 4 cycles + baseline x 4 cycles) versus ABVD (x 8 cycles) in Unfavorable stage III & IV patients stratified on the International Prognostic Score as IPS 3 or more.

1. Invitation to participate in the study

"The EORTC Lymphoma Group is initiating a research study on patients that have a disease similar to yours. The study will be conducted at the European – Canadian- Australian- New Zealand level under the supervision of physicians recognized as experts in this field of medicine. Today, you will be invited to take part to this research project after you are given full information about the study"

2. Introduction

Your disease is called Hodgkin lymphoma. It involves the lymph nodes. In your case, the work-up has shown the existence of spread-out lesions.

Its spontaneous evolution (when left untreated) is unfavourable, but most often this disease can be cured with existing treatments.

The aim of these treatments is to obtain the disappearance of all currently visible lesions, to prevent the disease coming back (sooner or later) and to limit the risks of late complications.

The value of such existing treatments has been proven for many years. The usual treatment is combination chemotherapy administered in 8 sequential cycles over 8 months. The current standard chemotherapy regimen, called “ABVD”, combines four drugs which have been used for several years (doxorubicin, bleomycin, vinblastine and dacarbazine).

Yet, it is still possible to improve their results and reduce their toxicity. Therefore it is necessary that all treatments be evaluated comparatively.

Previous studies suggested that a more intensive chemotherapy regimen, called BEACOPP (which associates bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) dosed every 3 weeks for 8 cycles during 6 months may improve the outcome of your disease. The first 4 cycles are given at higher doses (“escalated” BEACOPP) than the last 4 (BEACOPP “baseline”). Therefore this clinical research project designed as a phase III trial and involving approximately 600 patients, will compare the
standard ABVD treatment versus BEACOPP treatment, to evaluate which of the two treatments can improve the outcome of the patient.

3. Description of the research

To definitively establish if any of above-mentioned treatments are better, doctors all over Europe, Canada, Australia and New Zealand will treat their patients according to this clinical research project. Approximately, it will be needed 5 years to enter 600 patients and about one year after last patient has been entered to analyze data and have the results. Therefore, to answer this question, chance (this is called “randomization” and is done through a central computer) will decide if you will be treated with ABVD or BEACOPP regimen. Neither you nor your doctor can decide which treatment you will receive. Your chances to get ABVD or BEACOPP are 50% in both cases. You will be informed as to which sequence (arm) you have been assigned.

The main aim of this study is to compare which of the treatment is more effective, less toxic and giving more comfort to the patient.

In the ABVD arm medications are administered intravenously twice a month (one cycle) for 8 monthly cycles.

In the BEACOPP regimen, some drugs (bleomycin, etoposide, doxorubicin, cyclophosphamide and vincristine) are dosed intravenously (three intra venous injections during first week and one intra venous injection at the beginning of second week for each three-weekly cycle). Procarbazine and prednisone are dosed by oral route.

In both regimens new cycle starts every 22 days.

For receiving the treatment you can be admitted to the hospital, or you can receive in the “out-patient” clinic, meaning you do not have to stay over night after drug administration. This will depend on the hospital organization and your ability to tolerate the treatment.

Before treatment starts there will be medical checks will be done. These include physical examination, blood tests (blood counts, biochemistry, tests on viruses), radiological tests (including CT scan, scintigraphy and/or ultrasound), taking and examining a small piece of the tumor and a piece of the middle part of your bone (bone marrow biopsy). In some cases, when clinically indicated, a piece of liver can also be taken for examination. If needed, hormonal levels in your blood will also be measured. Lung and heart function will be evaluated. The chemotherapy can also induce sterility in men, therefore, as a precaution, a freezing of sperm is recommended.

To verify the initial diagnosis (done by the pathologist in your hospital), glass slides of tumor biopsy(s) (taken at the time of establishing the diagnosis) will be reviewed by a pathologist(s), expert(s) in field, using the microscope. Very often, the expert(s) will not be working in the hospital where you will receive protocol treatment, not even the same country. In some cases, when it is difficult to establish/confirm the diagnosis, a (frozen) sample of your tumor biopsy (taken at the time of establishing the diagnosis) will be asked (to the pathologist in your hospital) by the expert(s) pathologist(s). This material will be used to prepare new slides and perform additional diagnostic investigation.

Before each chemotherapy cycle there will be a physical check-up with blood counts check together with lung & heart function. X-ray of lung will be done if clinically indicated.

After cycle 4 and cycle 6 following examinations need to be done: blood check (counts and biochemistry), physical examination, radiological (CT scan) examination of your chest, stomach
& pelvis. In case bone marrow and/or liver have had disease before starting the treatment, they
will need to be examined again.

At the end of treatment (full treatment is 8 cycles) following will be done: blood check (counts
and biochemistry), physical examination, radiological (CT scan) examination of your chest,
stomach & pelvis. In case bone marrow and/or liver have had disease before starting the
treatment, they will need to be examined again.

After finishing the protocol treatment, you will need to come for a check every three months in
the first three years. In the years 4 and 5 check up will be every 6 months and after five years,
annual visits will be performed. During the visits following will be checked: blood check
(counts and biochemistry), physical examination, CT scan examination of your chest, stomach
& pelvis (this well be done 6, 12 and 24 months after finishing treatment).

All patients will be asked to fill out a questionnaire. The questionnaire should be completed at
before treatment starts, at the end of treatment and than annually, but no longer than 10 years.
This questionnaire asks you about how you feel and takes about 10 minutes to complete. It may
remind you of unpleasant things about your treatment or disease. Some of the questions are
personal, and you can refuse to answer these if you wish. The information that you provide is
for research purposes and will remain strictly confidential. The individuals (e.g. doctors, nurses,
etc) directly involved in your care will not usually see your responses to these questions -- if
you wish them to know this information, you will bring it to their attention.

4. Description of foreseeable risks and discomforts

The main adverse effects of the ABVD chemotherapy are: a reversible hair loss and transient
changes in blood cell counts (white and red cells, platelets). A low rate of white blood cells
(which are front line anti-infective mechanisms of the body), called neutropenia, during a few
days makes patients vulnerable to bacterial infections.

Drug vincristine can provoke weakness and tingling (in the extremities) and difficulties with
defecation.

The possible occurrence of low levels of red blood cells, which induces tiredness, can justify
that you undergo transfusions. The chemotherapy can also induce sterility in men. Female
patients, of childbearing potential, should take adequate contraceptive measures during the
whole treatment. However, as a precaution, a freezing of sperm and oocyte is recommended.

Lung problems (shortening of breath, cough) may occur, very rarely early on during bleomycin
administration, but sometimes later on, which justifies quitting smoking and pulmonary function
follow-up.

Heart problems (shortening of breath, quickly getting tired, cough, feet swelling) may occur in
the months or years after adriamycin administration, and this also justifies quitting smoking and
heart function follow-up.

BEACOPP treatment is more intensive, adverse effects can be more severe than with the
standard treatment. You may be offered to receive the first course of chemotherapy as an in-
patient clinic. The low white blood cell count needs to be prevented. This is done by
simultaneously using a drug (growth factors, G-CSF) which stimulates the production of white
blood cells and is therefore able to reduce the severity and the duration of neutropenia. To
prevent infection, you may be offered oral antibiotics. There can be allergic reactions. There is a
higher risk of infertility in men and of sterility and early menopause in women aged over 30
years. As a precaution, a freezing of sperm and oocyte is recommended. However during the
whole treatment, female patients of childbearing potential, should take adequate contraceptive
measures. Pulmonary and heart side effects are reduced as compared to ABVD. In very rare
instances, late effects may compromise blood cell production or even cause leukemia.
The side effects of chemotherapy will be closely monitored and the dose of drugs adjusted according to degree of symptoms. In some cases a drug will be removed from the regimen and possibly replaced by another. In very severe cases the protocol treatment will stop. Further treatment will be upon investigators discretion and in the best interest of the patient.

5. **Description of the ultimate goal of the research**

The present proposition is to assess whether treatment with BEACOPP can improve the outcome of the patient when compared to the 8 cycles of the standard ABVD regimen in patients with advanced Hodgkin's disease. At the same time, this research study will evaluate under which of the two treatments the disease can completely disappear and for how long, if patients live longer, if their quality of life can be improved, if other type of cancer will occur and which of the two treatments is less expensive.

6. **Expected benefits** (description of possible expected benefits)

No one knows if you will benefit from taking part in this study. Your cancer might shrink and you might feel better. There might be less chance of your cancer coming back. You might live longer.

The quality of your life might be better. These things cannot be predicted for you. Information from this study might help cancer patients in future.

If your disease becomes worse, if side effects become severe, if new information indicates that this treatment is not in your best interest, or your doctor feels that this treatment is no longer in your best interest, the treatment will be stopped. Further treatment will be discussed. If new side effects or information about your disease or treatment are discovered during the study, you will be told.

7. **Voluntary participation**

"*Your participation in this research trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. You are free to decide at all times without giving a reason that you no longer wish to participate in the trial. Withdrawal from the trial will not affect your subsequent treatment or relationship with your treating physician or the hospital staff in any way*"

8. **Data protection**

"*The trial involves the collection of information contained in your medical records and which relate to your disease. It is very important that the information collected is accurate and from time to time it may be checked against your medical records. Duly authorized persons (EORTC staff, national and/or foreign health authority representatives or certain persons from the company supplying the trial medication) may have access to your medical records. All information will be strictly confidential and your identity will never be divulged, you have the right to access this information according to the laws applicable in your country*"

"*To verify the initial diagnosis (done by the pathologist in your hospital), glass slides of tumor biopsy(s) (taken at the time of establishing the diagnosis) will be reviewed by a pathologist(s), expert(s) in field, using the microscope. Very often, the expert(s) will not be working in the hospital where you will receive protocol treatment, not even the same country. In some cases, when it is difficult to establish/confirm the diagnosis, a (frozen) sample of your tumor biopsy (taken at the time of establishing the diagnosis) will be asked (to the pathologist in your hospital) by the expert(s) pathologist(s). This material will be used to prepare new slides and perform additional diagnostic investigation*"
"This trial is conducted under the support of EORTC with the restricted financial participation of AMGEN"

"The EORTC, responsible for the conduct of this trial, has asked your treating physician to disclose any existing conflict of interest he/she may have as a result of his/her activities related to this trial. The EORTC has set up procedures to ensure the integrity of this process".

9. Insurance

The sponsor of the Study shall obtain a clinical trial insurance in accordance with the applicable legislation.

If you need to undergo another medical treatment, we advice you to inform the investigator to ensure this will not have any effect on your participation to the trial.

Everything has been done and will continue to be done to prevent additional health problems occurring as a result of your taking part in this trial.

10. Ethics Committee

This research protocol has been submitted to the ethics committee whose mission is to verify that all conditions with respect to your safety and rights are respected. Approval to this research has been given by the Ethics Committee of ____________ on ________________.

11. Contact persons

In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor: _____________________________

Hospital: _____________________________________

Telephone: ____________________________________

If you consent to join this trial, you will be given a telephone number at the hospital that you can contact at any time if you feel unwell or have further questions. Your family doctor will also be told about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions to your doctor if anything is not clear. You are entitled to keep a copy of this document after you and your doctor have signed it.
Acceptance of participation

(if a patient is younger than 18 years old, the informed consent must be obtained in compliance with the national regulations applicable in the country where the study is performed)

☐ I have been properly informed of the clinical research that is being proposed to me

☐ I have been properly informed of the clinical research that is being proposed to the child

☐ The child has been properly informed of the clinical research that is being proposed to him

☐ I have received a copy of the patient information sheet

☐ I have received a copy of the patient information sheet proposed to the child

☐ All my rights have been clearly explained

☐ All rights of the child have been clearly explained to me and to the child

☐ I have received a copy of the informed consent document

☐ I have received a copy of the informed consent document proposed to the child

☐ I accept to participate in the research entitled “Intergroup Hodgkin BEACOPP/ABVD study. A phase III randomized study on BEACOPP (escalated x 4 cycles + baseline x 4 cycles) versus ABVD (x 8 cycles) in Unfavorable stage III & IV patients stratified on the International Prognostic Score as IPS 3 or more” and registered under EORTC study number 20012. My participation is completely voluntary and I have the possibility to withdraw my consent at anytime without explanation. This will not affect my relationship with my treating physician. The data collected on my behalf will be strictly confidential and treated according to the "Directive on the protection of individuals with regard to the processing of personal data" and the local applicable laws.

My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law”.

☐ I accept that my child participates in the research entitled ____________________________ and registered under EORTC study number 20012. His/her participation is completely voluntary and I have the possibility to withdraw consent at anytime without explanation. This will not affect child’s relationship with his/her treating physician. The data collected on the child’s behalf will be strictly confidential and treated according to the "Directive on the protection of individuals with regard to the processing of personal data" and the local applicable laws.

My consent does not discharge the organizers of the research from their responsibilities and child keep all his/her rights guaranteed by the law”.

☐ I have been informed that the data collected may be used in the future for any scientific purpose while confidentiality will be ensured

☐ I have been informed that child’s data collected may be used in the future for any scientific purpose while confidentiality will be ensured
Patient's name: __________________________

Patient's signature: ___________________ Date: ________________

Parent’s/legal representative’s name: __________________________

Parent’s/legal representative’s signature:___________________Date: ________________

Person designated by the investigator to participate in the informed consent process:

Name: ________________________________

Signature: ______________________________ Date: ________________

Investigator's name: _____________________

Title/Position: __________________________

Investigator's Signature: ________________ Date: ________________

This document has been prepared taking into account:
Appendix G: GELA Group Specific Appendix

This protocol is coordinated by EORTC and follows the standard EORTC sequence of chapters. The chapters 1-14 and 23 of the protocol are common to all the groups. All scientific, practical and administrative aspects of the protocol specific to GELA are included under the GELA Appendix of the protocol and instead of chapters 15-22 (except specified otherwise in the following appendix).

Since GELA is the legal sponsor for EORTC French investigators, they should also refer to this appendix whenever GELA specific sections are mentioned in the main protocol and instead of chapters 15 through 22 (except specified otherwise in the following appendix).

Contact addresses

Co-Chairman &
GELA Study coordinator:
Dr. Marine Divine
GELA Data Center
Service d’Hématologie
Hôpital Henri Mondor
51 avenue du Maréchal de Lattre de Tassigny
94000 Créteil, France
Phone: +33 1 49 81 21 71 or 74
Fax: +33 1 49 81 21 71
E-mail: marine.divine@hmn.ap-hop-paris.fr

GELA clinical trial office:
Responsable du Bureau des Etudes
GELA-RC
Marie-Caroline Fiore
Phone: +33 4 72 66 93 33
Fax: +33 4 72 66 93 71
e-mail: gelarc@chu-lyon.fr
1 Scientific matters considered as group specific and not detailed in the protocol.

1.1 Drug/treatment

G-CSF: Lenograstim, Laboratoire Chugai Pharma France

1.2 Economic evaluation

Economic evaluation will be performed by Pr Isabelle Durand-Zaleski (Unité de Santé Publique, Hôpital Henri Mondor, Créteil, France). Centers participating in the economic evaluation are those belonging to the AP-HP which shares common cost-accounting systems. Other hospitals will be recruited on a voluntary basis, during the first investigator meeting. The prerequisite for participating in the economic study is the availability of detailed cost data for each unit in the hospital.

1.3 Parallel study

All patients with clinical stage III or IV, whatever the International Prognostic Score (IPS), will be included in the study, so called “Protocol H3-4” for the French investigators. The randomization will be stratified according to this score, leading to distinguish standard-risk (IPS 0-2) and high-risk (IPS ≥ 3) patients.

2 Investigator authorization procedure

All regulatory procedures must be completed in cooperation with the GELA Data Center before the investigators can be authorized to register patients in this trial.

Each time an institution has become authorized to enter patients in this trial, the GELA Data Center will inform the EORTC Data Center. The EORTC Data Center will provide immediately the GELA Data Center with the EORTC institution number for the concerned investigator.

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the Data Center:

♦ a commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,

♦ a copy of the letter of acceptance of the protocol by their national (for colleagues from Belgium and Switzerland) ethics committee,

♦ a signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared by the commitment form.

and, if the following documents are not yet available at the Data Center:

♦ their updated Curriculum Vitae,

♦ the list of the normal ranges, in their own institution, of all laboratory data required by the protocol,

♦ the list of their staff members authorized to sign case report forms, with a sample of each authorized signature.

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as
all the above mentioned documents are available at the Data Center

♦ all applicable national health authorities requirements are fulfilled

For the EORTC French Investigators, the EORTC Data Center can provide GELA with CVs, laboratory normal ranges and the laboratory accreditation if they have been collected recently.

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

### 3 Patient randomization procedure

Patient registration will only be accepted from authorized investigators (see "Authorization procedure").

An exhaustive list of questions to be answered during the randomization procedure is included in the EORTC Registration Checklist. The responsible investigator should complete The EORTC Registration Checklist and all the baseline forms before the patient is randomized.

All GELA and EORTC French Investigators should send the randomization checklist to the GELA Secretariat by fax:

**Secrétariat de randomisation du GELA H3-4**

Centre Hayem, Hôpital Saint Louis,

fax (33) 1 42 49 99 72

As soon as this form is received, the patient will be randomized by GELA Secretariat directly on the EORTC Data Center.

The GELA Secretariat will randomize patients as described in the chapter 16 of the main protocol.

Concerning the Group affiliation question:

Primary group affiliation: for all the investigators participating on behalf of GELA, the primary group affiliation is "GELA".

Secondary group affiliation:

♦ for GELA investigators that are not members of the EORTC Lymphoma group, the secondary affiliation should not be completed

♦ for the EORTC French investigators participating on behalf of GELA because of the legal sponsoring, the secondary affiliation must be completed "EORTC"

♦ for the Investigators members of both GELA and the EORTC Lymphoma group, the secondary affiliation can be completed "EORTC" if they wish their patients to be counted also for the EORTC membership (to be clearly indicated when contacting the GELA Secretariat).

At the end of this procedure, the sequential identification number and the treatment will be allocated to the patient. The GELA Secretariat will receive this information by an automatic E-mail and will forward it immediately to the investigators and to the GELA Data Center for H3-4 in Créteil (Dr. Marine Diviné, study coordinator).

This sequential identification number of patient has to be recorded on all the forms. All the forms should be then sent to the GELA Data Center in Créteil, which will send it to the EORTC Data Center.
4 Procedures for collecting data

All the Investigators participating on behalf of GELA will send all the forms to:

Dr. Marine Diviné  
GELA Data Center  
Hôpital Henri Mondor, Service d’Hématologie Clinique  
51, avenue du Maréchal de Lattre de Tassigny, 94 000 Créteil, France

The GELA Data Center will follow a “mail-box” procedure for this trial. This means that:

♦ Signed original CRFs will be collected by the GELA Data Center and sent regularly to the EORTC Data Center according to the form flow schedule (provided with the CRFs)
♦ Investigators will not be allowed to send CRFs directly to the EORTC Data Center
♦ The GELA Data Center will not modify the forms nor enter them into the computer
♦ The EORTC Data Center will enter the data in the computer for quality control and analysis. When necessary, queries will be transmitted to the GELA Data Center, which will send them to the investigators. The GELA Data Center will then send the reply of the investigators back to the EORTC Data Center.

Besides the above, the procedures to guarantee the quality control (other than the collection and the verification of data, i.e. verification of the signature, data timeliness) should be applied as usual to all GELA and EORTC French investigators.

However, concerning the EORTC French investigators, if any procedure is not followed as requested or if any quality remark should be formulated, this will be addressed first to the EORTC Data Center.

Inversely, if the EORTC has any general comments on the compliance of GELA investigators to the protocol, this will be addressed to the GELA Data Center.

5 Reporting adverse events

♦ For all definitions of AE, refer to the main protocol (chapter 18).
♦ For the reporting of SAE (and possible SADR occurring after the 30-day period), the same process as in the main protocol should be used (see chapter 18).
♦ Investigators should complete the EORTC SAE form 89 (the header of this form will include the name of GELA, GELA’s protocol name and adequate instructions; will be provided with the main set of CRFs) and send it following the deadlines described in the chapter 18 to:

  Centre de gestion à Créteil  
  Fax: +33 1 49 81 21 71

♦ GELA Data Center will forward the SAEs to the Health Agency, to the national Ethical Review Board, and to the EORTC safety desk within 24 hours.

6 Quality assurance

6.1 Control of data consistency

The GELA Data Center will not control the consistency of the data.
6.2 Central review of histology

As for all studies by the GELA, a central pathology review will be performed under the coordination by

Pr. Josée Audouin
Laboratoire d’Anatomo-pathologie de l’Hôtel-Dieu
1, place du Parvis Notre-Dame, 75 181 Paris Cedex 04
Tel: (33) 1 42 34 82 82; Fax: (33) 1 42 34 86 41
E-mail: anapath.hd@htd.ap-hop-paris.fr

7 Ethical considerations

See the main protocol (chapter 20).

8 Administrative responsibilities

8.1 The study coordinator

The Study Coordinator of GELA is Co-Chairman of this trial. Together with the Study Coordinator (EORTC) and in cooperation with the EORTC Data Center Team, she will be responsible for:

♦ writing the protocol
♦ reviewing all case report forms (documenting her review on evaluation forms)
♦ discussing the contents of the reports
♦ publishing the study results.

She will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

GELA Study coordinator (Study Co-Chairman):

Dr. Marine Divine
Hôpital Henri Mondor, Service d’Hématologie Clinique
51, avenue du Maréchal de Lattre de Tassigny, 94 000 Créteil, France
Phone: +33 1 49 81 21 71 or 74 / Fax: +33 1 49 81 21 71
E-mail: marine.divine@hmn.ap-hop-paris.fr

8.2 The Data Center

The GELA Data Center is responsible for all the administrative procedures required for the trial following the normal procedures of GELA and respecting the present appendix.

The data center is also responsible, as an intermediate, to guarantee the fluent communication between the EORTC Data Center and the Investigators participating on behalf of GELA.

GELA Data Center for H3-4 Protocol
Hôpital Henri Mondor, Service d’Hématologie Clinique
51, avenue du Maréchal de Lattre de Tassigny, 94 000 Créteil, France
Phone/ Fax: +33 1 49 81 21 71
8.3 The GELA group

GELA is responsible as a group to guarantee the general compliance of their members to procedures described in this appendix. All questions concerning membership in the group should be addressed to the chairman and/or secretaries of the group.

President:
Pr. Felix Reyes, Hôpital Henri Mondor 94 000 Créteil
Tel (33) 1 49 81 20 51, Fax (33) 1 49 81 20 67, E-mail felix.reyes@hmn.ap-hop-paris.fr

Past-President:
Pr Christian Gisselbrecht, Hôpital Saint-Louis 75475 Paris Cedex10

Treasurer
Pr Bertrand Coiffer, Hôpital Lyon Sud 69495 Pierre Bénite Cedex

Vice-presidents
Pr André Bosly, Clinique Universitaire de Mont-Godine (Belgique)
Pr Gilles Salles, Hôpital Lyon Sud 69495 Pierre Bénite Cedex

Secretaries
Pr Christian Bastard, Centre Henri Becquerel, 76038 Rouen Cedex
Pr Philippe Gaulard, Hôpital Henri Mondor 94 000 Créteil
Pr Eric Lepage, Hôpital Henri Mondor 94 000 Créteil
Pr Hervé Tilly, Centre Henri Becquerel, 76038 Rouen Cedex

9 Trial sponsorship and financing

GELA is a Legal Sponsor for all French patients (patients entered in the trial by GELA members and by the EORTC French investigators). This trial is financed by public institutional grants resulting from the Ministry of Health (Programme Hospitalier de Recherche Clinique 2001N/Ref AOMO 1066) and funds provided by Chugai Pharma France.
All EORTC French investigators will be accepted to participate to the trial if all documents required in the chapter 2 of the present appendix were provided.

**10 Trial Insurance for GELA**

GELA contracted the following insurance for the needs of the trial:

GERLING n° 2002134.

**11 Patient information sheet and informed consent**
Lettre d'information au patient majeur

Titre du protocole de recherche :
Essai prospectif randomisé dans les stades III-IV de la maladie de Hodgkin : évaluation comparative de l'efficacité et de la toxicité de deux modalités de chimiothérapie, l'ABVD et le BEACOPP.

Étude de l'Intergroupe GELA / EORTC

Madame, Monsieur,

L'analyse du prélèvement qui vous a été fait a permis de porter le diagnostic de maladie de Hodgkin. Il s'agit d'une maladie ganglionnaire. Dans votre cas, le bilan d'extension a conclu à l'existence de lésions disséminées.

L'évolution spontanée de la maladie sans traitement est défavorable, mais elle guérit le plus souvent avec les traitements actuels.

Le but de ces traitements est d'obtenir la disparition de toutes les lésions actuellement visibles de la maladie, de prévenir la survenue de récidive ultérieure, de limiter les risques de complications tardives. L'efficacité des traitements actuels est prouvée depuis des années. Le traitement habituel est une chimiothérapie délivrée en 8 cures séquentielles sur 8 mois. La chimiothérapie de référence (appelée ABVD) associe des médicaments utilisés depuis plusieurs années (doxorubicine, bléomycine, vinblastine et dacarbazine)

Cependant, des progrès sont encore possibles pour améliorer les résultats et diminuer les toxicités (effets indésirables) du traitement. Il est donc nécessaire que tous les traitements soient évalués comparativement.

De récentes études suggèrent qu'une chimiothérapie plus intensive, appelée BEACOPP (association de bléomycine, étoposide, doxorubicine, cyclophosphamide, vincristine, procarbazine et prednison) administrée toutes les 3 semaines, pour un total de 8 cycles sur 6 mois, pourrait présenter un avantage pour traiter votre maladie. Les 4 premiers cycles sont administrés à des doses plus élevées (BEACOPP renforcé) que les 4 cycles suivants (BEACOPP standard) Par conséquent, ce protocole d'essai clinique de phase III qui inclura 600 patients environ va comparer le traitement standard (ABVD) au BEACOPP pour déterminer lequel est le plus efficace.

Pour déterminer quel traitement, parmi les 2 sus-cités, est le plus efficace, des médecins d'Europe, Canada, Australie et Nouvelle-Zélande vont traiter leurs patients selon ce protocole d'étude. Environ 600 patients seront inclus sur une période de 5 ans. L'analyse des résultats sera faite 1 an après l'inclusion du dernier patient. En l'absence de données disponibles permettant d'affirmer qu'un des deux traitements est supérieur à l'autre, votre traitement sera défini selon une liste préétablie de façon aléatoire ( tirage au sort), le traitement qui vous sera assigné (ABVD ou BEACOPP) ne pourra être déterminé d'avance. Ni vous ni votre médecin ne pourront choisir le traitement que vous recevrez.

Le but de cet essai est de déterminer quel est le traitement le plus efficace, le moins toxique et qui vous procure la meilleure qualité de vie possible.

Dans le traitement ABVD, les médicaments sont administrés par voie intraveineuse tous les 15 jours pour un total de 8 cycles mensuels.
Dans le traitement BEACOPP, certains médicaments (bléomycine, étoposide, doxorubicine, cyclophosphamide et vincristine) sont administrés par voie intraveineuse (trois perfusions pendant la première semaine et une perfusion au début de la deuxième semaine pour chaque cycle de trois semaine) ; la procarbazine et le prednisone sont administrés par voie orale. Un médicament, le lénograstime, destiné à stimuler la production de vos globules blancs vous sera également administré par voie sous-cutanée, à partir du 9ème jour de chaque cycle de chimiothérapie et durant environ une semaine.

Quel que soit le traitement que vous recevrez, il pourra se faire en hospitalisation classique ou en hôpital de jour, cela dépendra de l'organisation de l'unité de soins et de votre tolérance au traitement.

Avant de débuter le traitement, un bilan vous sera fait, il comprend un examen clinique, des tests sanguins et des examens radiologiques (scanner, scintigraphie des os, échographie). Un prélèvement tumoral, un prélèvement de moelle osseuse (biopsie de la moelle osseuse) et dans certains cas, un prélèvement de tissu hépatique seront pratiqués.

Des échantillons de sang seront également prélevés mais analysés ultérieurement pour l'étude de nouveaux marqueurs d'évolutivité de la maladie de Hodgkin. Ces échantillons de sang seront stockés sous la responsabilité de votre médecin, et ne pourront pas être, ainsi que leurs résultats, utilisés ou confiés à un tiers pour d'autres fins que ceux de la présente étude.

Si nécessaire des dosages hormonaux sanguins seront faits. Les fonctions respiratoires et cardiaques seront évaluées.

Avant le début de chaque cycle de chimiothérapie, vous aurez un examen clinique, un prélèvement sanguin (10 à 15 ml de sang), une évaluation de la fonction cardiaque et respiratoire et si nécessaire une radiographie du thorax.

Quel que soit le traitement que vous recevrez, un bilan d'évaluation sera fait après 4 et 6 cures de chimiothérapie, et à la fin du traitement. Il comprendra un examen clinique, un prélèvement sanguin (10 à 15 ml de sang), des examens radiologiques (scanner) du thorax, de l'abdomen et du pelvis. En cas d'enravissement initial de la moelle osseuse et/ou du foie, ces organes seront de nouveau examinés.

Après la fin du traitement, vous aurez des consultations de contrôle tous les 3 mois pendant 3 ans, tous les 6 mois pendant la 4ème et 5ème années puis tous les ans après la 5ème année. Lors de ces consultations vous aurez un examen clinique et un prélèvement sanguin. Un scanner du thorax, de l'abdomen et du pelvis sera pratiqué 6, 12, et 24 mois après la fin du traitement ; en cas d'image résiduelle, votre médecin peut vous proposer une surveillance plus rapprochée ou prolongée s'il juge que c'est dans votre intérêt.

Afin de pouvoir évaluer l'effet du traitement sur votre qualité de vie, il vous est demandé de compléter un questionnaire (il faut environ 10 minutes pour le remplir) avant le début du traitement, à la fin du traitement puis tous les ans (au maximum 10 ans après la fin du traitement).

Les principaux effets indésirables de la chimiothérapie classique (ABVD) sont une perte de cheveux réversible et une baisse transitoire de quelques jours des cellules du sang (globules blancs, globules rouges et plaquettes). La baisse des globules blancs (neutropénie) vous expose à un risque d'infection bactérienne. La survenue d'une éventuelle anémie responsable d'une fatigue, peut justifier la réalisation de transfusions. La vincristine peut provoquer une faiblesse musculaire transitoire, des fourmillements des extrémités et une constipation. La chimiothérapie peut aussi entraîner une stérilité chez l'homme. Par précaution, une congélation du sperme est proposée. Les femmes en âge de procréer doivent recevoir une contraception efficace durant toute la durée du traitement.
Rarement, des effets secondaires respiratoires (toux, essoufflement) peuvent survenir au cours des perfusions de bléomycine ou à distance, justifiant l'arrêt du tabac et un suivi de la fonction respiratoire. Des effets secondaires cardiaques (essoufflement, fatigue après des efforts mineurs, toux, œdèmes des membres inférieurs) peuvent survenir dans les mois ou années suivant l'administration d'adriamycine, justifiant l'arrêt du tabac et un suivi de la fonction cardiaque.

Le traitement BEACOPP étant plus intensif, ses effets indésirables peuvent être plus marqués que ceux du traitement habituel. Il vous sera proposé de recevoir la 1ère cure en hospitalisation.

La baisse des globules blancs du sang pourra être prévenue par l'utilisation simultanée du lénochrégostim, facteur stimulant la production des globules blancs et donc capable de diminuer l'intensité et la durée de cette baisse. Des douleurs osseuses transitoires peuvent être liées à l'injection de ce médicament ; elles sont réversibles sous antalgiques. Il pourra vous être proposé une antibiothérapie orale pour prévenir la survenue de certaines infections microbiennes.

Des réactions allergiques peuvent survenir.

Le risque de stérilité est plus marqué dans les 2 sexes. Les femmes âgées de plus de 30 ans sont exposées au risque de survenue de ménopause précoce. Les femmes en âge de procréer doivent recevoir une contraception efficace durant toute la durée du traitement. Chez l'homme une congélation du sperme est proposée.

Le risque de survenue d'effets secondaires pulmonaires et/ou cardiaques sont moindres qu'avec l'ABVD. Exceptionnellement (dans moins de 2% des cas), des effets secondaires tardifs peuvent compromettre la production des globules du sang et exposer à la survenue d'une leucémie.

La survenue d'effets secondaires sera étroitement surveillée et si besoin, une réduction des doses des médicaments en cause sera effectuée. Si nécessaire un médicament sera exclu du traitement et remplacé par un autre. En cas de survenue d'effet secondaire grave le traitement peut être définitivement arrêté et un autre traitement vous sera proposé. De même votre médecin garde la possibilité d'interrompre le traitement s'il juge que c'est dans votre intérêt. Toute nouvelle information, qu'elle qu'en soit la nature, concernant les traitements à l'étude et qui serait susceptible d'influencer votre décision de continuer à participer à l'étude vous sera communiquée dès qu'elle sera connue.

L'objet du présent protocole est de déterminer si le traitement à l'étude (BEACOPP) améliore le devenir des patients comparé au traitement standard (8 cures d'ABVD)

Le bénéfice possible attendu réside en la disparition des signes de la maladie, une meilleure qualité de vie et la réduction du risque de récidive de la maladie. Les résultats recueillis pourront éventuellement servir pour traiter d'autres patients dans le futur.

Votre participation à ce protocole est totalement volontaire. Votre acceptation ou votre refus ne modifieront en rien les rapports que vous aurez avec votre médecin qui continuera de vous proposer les soins qui paraissent les plus adaptés à votre état de santé. Vous pouvez si vous le désirez interrompre le traitement à tout moment. Vous pouvez à tout moment demander des informations complémentaires au Dr ……………………………..
Conformément à la législation, le Groupe d’Etude des Lymphomes de l’Adulte (GELA), promoteur de cette étude, a pris toutes les dispositions prévues par la loi pour la protection des personnes se prêtant à la recherche biomédicale (Loi Huriet n° 88-1138 du 20/12/88 modifiée par la loi du 23/01/90) Cette recherche a reçu le 12 juillet 2002 l’avis favorable du Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale - Créteil Henri Mondor. Le GELA a souscrit une assurance responsabilité civile pour cette étude.

Cet essai est financé par des fonds publics provenant du Ministère de la santé (Programme Hospitalier de Recherche Clinique 2001 N/Ref AOMO 1066) et une aide complémentaire de soutien à la recherche clinique accordée par le laboratoire Chugai Pharma France

Votre participation ne peut qu’être volontaire, aussi nous vous demandons si vous y consentez de signer le formulaire de consentement écrit selon les exigences légales.

Le médecin responsable
Formulaire de consentement éclairé pour patient majeur

Je soussigné (e)………………………………………………………………………………………………. Demeurant à ………………………………….
Certifie que le Docteur …………………………………………………………………………………………………. m’a proposé de participer à une recherche intitulée «Essai prospectif randomisé dans les stades III-IV de la maladie de Hodgkin : Evaluation comparative de l’efficacité et de la toxicité de deux modalités de chimiothérapie, l’ABVD et le BEACOPP ».
Le médecin m’a précisé que je suis libre d’accepter ou de refuser de participer à cette recherche. Cela ne changera pas nos relations pour mon traitement.
Afin d’éclairer ma décision, j’ai reçu et bien compris les informations suivantes qui m’ont été données par écrit et oralement. Mon médecin m’a expliqué ma maladie, son stade actuel et les différents traitements indiqués, leurs avantages et leurs inconvenients respectifs. L’étude proposée vise à comparer l’efficacité et les effets secondaires du traitement par chimiothérapie habituel (ABVD) à un traitement plus intensif (BEACOPP) dans ma maladie. Ces deux traitements médicaux sont administrés selon deux schémas différents pendant 6 à 8 mois. Le traitement plus intensif pourrait être associé à des effets secondaires plus importants que le traitement habituel, mais il pourrait aussi être plus efficace. La supériorité d’un traitement sur l’autre ne pourra être évaluée qu’au terme de cette étude. Je serai régulièrement suivi pendant cette étude et j’ai pris connaissance des visites et examens médicaux nécessaires à son bon déroulement.
Cette recherche a reçu l’avis favorable du Comité Consultatif de Protection des Personnes participant à une recherche Biomédicale de Créteil Henri Mondor, le --/--/--.
Le promoteur de cette recherche, le Groupe d’Etude des Lymphomes de l’Adulte (GELA) a contracté une assurance (Société GERLING, 111 rue de Longchamp, 75116 Paris ; N° 2002134) conformément à la loi du 20 décembre 1988 modifiée (Livre IIBis du Code de la Santé Publique)
J’accepte que les données nominatives me concernant recueillies à l’occasion de cette recherche puissent faire l’objet d’un traitement automatisé par les organisateurs de la recherche.
Le droit d’accès et de rectification prévu par la loi « Informatique et Libertés » (Loi du 6 janvier 1978 modifiée le 1er juillet 1994 - article 40-4) s’exerce à tout moment auprès des responsables de la recherche. Pour toutes les informations de nature médicale, j’exercerai ce droit par l’intermédiaire d’un médecin de mon choix.
Les données recueillies demeureront strictement confidentielles. Je n’autorise leur consultation que par l’équipe médicale, les personnes dûment mandatées par le promoteur de la recherche et éventuellement par des représentants des autorités administratives de Santé, tous soumis au secret professionnel (article 40-3 même loi)
Je pourrai à tout moment demander toute information complémentaire au Dr (NOM PRENOM)………………………………………………………………………………………………(ADRESSE)………………………………………………………………………………………………(N°TELEPHONE)………………………………………………………………………………………………(E-MAIL...) ……………………………
J’ACCEPTE LIBREMENT ET VOLONTAIREMENT DE PARTICIPER A CETTE ETUDE MEDICALE DANS LES CONDITIONS DECrites CI-DESSUS.
Mon consentement ne décharge en rien l’investigateur et le promoteur de leurs responsabilités et je conserve tous mes droits garantis par la loi.

Je suis conscient que je peux retirer mon consentement à tout moment, quelles que soient mes raisons. Le fait de ne plus participer à cette recherche ne portera pas atteinte à mes relations avec le médecin investigateur qui continuera à me soigner dans les meilleures conditions suivant les moyens habituels et ne me privera pas de mes droits.

Je garde un exemplaire de la feuille d’information que m’a remise le Dr (NOM PRENOM) .......................................... et du présent consentement

Fait à , le
NOM PRENOM de la personne donnant le consentement :

Signature

Je, soussigné Dr (NOM PRENOM) ........................................ certifie que (NOM PRENOM) ........................................ a donné ce jour son consentement informé, libre et révocable à la recherche nommée ci-dessus.
Le Signature :
Lettre d'information aux parents d'un patient mineur

Titre du protocole de recherche :
Essai prospectif randomisé dans les stades III-IV de la maladie de Hodgkin : évaluation comparative de l'efficacité et de la toxicité de deux modalités de chimiothérapie, l'ABVD et le BEACOPP.

Étude de l'Intergroupe GELA / EORTC

Madame, Monsieur,

L'analyse du prélèvement qui a été fait à votre enfant a permis de porter le diagnostic de maladie de Hodgkin. Il s'agit d'une maladie ganglionnaire. Dans son cas, le bilan d'extension a conclu à l'existence de lésions disséminées.

L'évolution spontanée de la maladie sans traitement est défavorable, mais elle guérit le plus souvent avec les traitements actuels.

Le but de ces traitements est d'obtenir la disparition de toutes les lésions actuellement visibles de la maladie, de prévenir la survenue de récidive ultérieure, de limiter les risques de complications tardives. L'efficacité des traitements actuels est prouvée depuis des années.

Le traitement habituel est une chimiothérapie délivrée en 8 cures séquentielles sur 8 mois. La chimiothérapie de référence (appelée ABVD) associe des médicaments utilisés depuis plusieurs années (doxorubicine, bléomycine, vinblastine et dacarbazine)

Cependant, des progrès sont encore possibles pour améliorer les résultats et diminuer les toxicités (effets indésirables) du traitement. Il est donc nécessaire que tous les traitements soient évalués comparativement.

De récentes études suggèrent qu'une chimiothérapie plus intensive, appelée BEACOPP (association de bléomycine, étoposide, doxorubicine, cyclophosphamide, vincristine, procarbazine et prednisone) administrée toutes les 3 semaines, pour un total de 8 cycles sur 6 mois, pourrait présenter un avantage pour traiter votre maladie. Les 4 premiers cycles sont administrés à des doses plus élevées (BEACOPP renforcé) que les 4 cycles suivants (BEACOPP standard) Par conséquent, ce protocole d'essai clinique de phase III qui inclura 600 patients environ va comparer le traitement standard (ABVD) au BEACOPP pour déterminer lequel est le plus efficace.

Pour déterminer quel traitement, parmi les 2 sus-cités, est le plus efficace, des médecins d'Europe, Canada, Australie et Nouvelle Zélande vont traiter leurs patients selon ce protocole d'étude. Environ 600 patients seront inclus sur une période de 5 ans. L'analyse des résultats sera faite 1 an après l'inclusion du dernier patient. En l'absence de données disponibles permettant d'affirmer qu'un des deux traitements est supérieur à l'autre, votre traitement sera défini selon une liste préétablie de façon aléatoire (tirage au sort), le traitement qui sera assigné à votre enfant (ABVD ou BEACOPP) ne pourra être déterminé d'avance. Ni vous ni le médecin ne pourront choisir le traitement qu'il recevra.

Le but de cet essai est de déterminer quel est le traitement le plus efficace, le moins toxique et qui lui procure la meilleure qualité de vie possible.

Dans le traitement ABVD, les médicaments sont administrés par voie intraveineuse tous les 15 jours pour un total de 8 cycles mensuels.
Dans le traitement BEACOPP, certains médicaments (bléomycine, étoside, doxorubicine, cyclophosphamide et vincristine) sont administrés par voie intraveineuse (trois perfusions pendant la première semaine et une perfusion au début de la deuxième semaine pour chaque cycle de trois semaine) ; la procarbazine et le prednisone sont administrés par voie orale. Un médicament, le léno-grastime, destiné à stimuler la production de vos globules blancs sera également administré par voie sous-cutanée, à partir du 9ème jour de chaque cycle de chimiothérapie et durant environ une semaine.

Quel que soit le traitement qu’il recevra, il pourra se faire en hospitalisation classique ou en hôpital de jour, cela dépendra de l’organisation de l’unité de soins et de la tolérance de votre enfant au traitement.

Avant de débuter le traitement, un bilan lui sera fait, il comprend un examen clinique, des tests sanguins et des examens radiologiques (scanner, scintigraphie des os, échographie). Un prélèvement tumoral, un prélèvement de moelle osseuse (biopsie de la moelle osseuse) et dans certains cas, un prélèvement de tissu hépatique seront pratiqués.

Des échantillons de sang seront également prélevés mais analysés ultérieurement pour l’étude de nouveaux marqueurs d’évolivité de la maladie de Hodgkin. Ces échantillons de sang seront stockés sous la responsabilité de votre médecin, et ne pourront pas être, ainsi que leurs résultats, utilisés ou confiés à un tiers pour d’autres fins que ceux de la présente étude.

Si nécessaire des dosages hormonaux sanguins seront faits. Les fonctions respiratoires et cardiaques seront évaluées.

Avant le début de chaque cycle de chimiothérapie, votre enfant aura un examen clinique, un prélèvement sanguin (10 à 15 ml de sang), une évaluation de la fonction cardiaque et respiratoire et si nécessaire une radiographie du thorax.

Quel que soit le traitement qu’il recevra, un bilan d’évaluation sera fait après 4 et 6 cycles de chimiothérapie et à la fin du traitement. Il comprendra un examen clinique, un prélèvement sanguin (10 à 15 ml de sang), des examens radiologiques (scanner) du thorax, de l’abdomen et du pelvis. En cas d’envahissement initial de la moelle osseuse et/ou du foie, ces organes seront de nouveau examinés.

Après la fin du traitement, il aura des consultations de contrôle tous les 3 mois pendant 3 ans, tous les 6 mois pendant la 4ème et 5ème années puis tous les ans après la 5ème année. Lors de ces consultations il aura un examen clinique et un prélèvement sanguin. Un scanner du thorax, de l’abdomen et du pelvis sera pratiqué 6, 12. et 24 mois après la fin du traitement ; en cas d’image résiduelle, votre médecin peut vous proposer une surveillance plus rapprochée ou prolongée s’il juge que c’est dans votre intérêt.

Afin de pouvoir évaluer l’effet du traitement sur la qualité de vie de votre enfant, il lui est demandé de compléter un questionnaire (il faut environ 10 minutes pour le remplir) avant le début du traitement, à la fin du traitement puis tous les ans (au maximum 10 ans après la fin du traitement).

Les principaux effets indésirables de la chimiothérapie classique (ABVD) sont une perte de cheveux réversible et une baisse transitoire de quelques jours des cellules du sang (globules blancs, globules rouges et plaquettes). La baisse des globules blancs (neutropénie) expose votre enfant à un risque d’infection bactérienne. La survenue d’une éventuelle anémie responsable d’une fatigue, peut justifier la réalisation de transfusions. La vincristine peut provoquer une faiblesse musculaire transitoire, des fourmillements des extrémités et une constipation.

Rarement, des effets secondaires respiratoires (toux, essoufflement) peuvent survenir au cours des perfusions de bléomycine ou à distance, justifiant l’arrêt du tabac et un suivi de la fonction respiratoire.
Des effets secondaires cardiaques (essoufflement, fatigue après des efforts mineurs, œdèmes des membres inférieurs) peuvent survenir dans les mois ou années suivant l'administration d'adriamycine, justifiant l'arrêt du tabac et un suivi de la fonction cardiaque.

Le traitement BEACOPP étant plus intensif, ses effets indésirables peuvent être plus marqués que ceux du traitement habituel. Il lui sera proposé de recevoir la 1ère cure en hospitalisation si nécessaire.

La baisse des globules blancs du sang pourra être prévenue par l'utilisation simultanée du lénostrastimine, facteur stimulant la production des globules blancs et donc capable de diminuer l'intensité et la durée de cette baisse. Ce médicament peut induire des douleurs osseuses transitoires, réversibles sous antalgiques.

Il pourra lui être proposé une antibiothérapie orale pour prévenir la survenue d'infections bactériennes.

Des réactions allergiques peuvent survenir.

Le risque de survenue d'effets secondaires pulmonaires et/ou cardiaques sont moindres qu'avec l'ABVD.

Exceptionnellement (dans moins de 2% des cas), des effets secondaires tardifs peuvent compromettre la production des globules du sang et exposer à la survenue d’une leucémie.

La survenue d'effets secondaires sera étroitement surveillée et si besoin une réduction des doses des médicaments en cause sera effectuée. Si nécessaire un médicament sera exclu du traitement et remplacé par un autre. En cas de survenue d'effet secondaire grave le traitement peut être définitivement arrêté et un autre traitement lui sera proposé. De même, son médecin garde la possibilité d'interrompre le traitement s'il juge que c'est dans son intérêt. Toute nouvelle information, qu'elle qu'en soit la nature, concernant les traitements à l'étude et qui serait susceptible d’influencer votre décision de participer à l'étude vous sera communiquée dès qu’elle sera connue.

L'objet du présent protocole est de déterminer si le traitement à l'étude (BEACOPP) améliore le devenir des patients comparé au traitement standard (8 cures d'ABVD)

Le bénéfice possible attendu réside en la disparition des signes de la maladie, une meilleure qualité de vie et la réduction du risque de récidive de la maladie. Les résultats recueillis pourront éventuellement servir pour traiter d'autres patients dans le futur

La participation de votre enfant à ce protocole est totalement volontaire. Votre acceptation ou votre refus ne modifieront en rien les rapports que vous et votre enfant aurez avec son médecin qui continuera de lui proposer les soins qui paraissent les plus adaptés à son état de santé. Vous pouvez si vous le désirez interrompre le traitement à tout moment. Vous pouvez à tout moment demander des informations complémentaires au Dr ………………………..

Votre droit d’accès et de rectification prévu par la loi « Informatique et Libertés » (Loi du 6 janvier 1978 modifiée le 1er juillet 1994 - article 40-4) s’exerce à tout moment auprès des responsables de la recherche. Pour toutes les informations de nature médicale, vous exercerez ce droit par l’intermédiaire d’un médecin de votre choix.

Les données recueillies demeureront strictement confidentielles. Ne pourront y accéder que les membres de l’équipe médicale, les personnes dûment mandatées par le promoteur de la recherche et éventuellement par des représentants des autorités administratives de Santé, tous soumis au secret professionnel (article 40-3 même loi)

Conformément à la législation, le Groupe d’Etude des Lymphomes de l’Adulte (GELA), promoteur de cette étude, a pris toutes les dispositions prévues par la loi pour la protection des personnes se prêtant à la recherche biomédicale (Loi Huriet n° 88-1138 du 20/12/88 modifiée par la loi du 23/01/90) Cette recherche a reçu le 12 juillet 2002 l'avis favorable du Comité
Consultatif de Protection des Personnes dans la Recherche Biomédicale - Créteil Henri Mondor. Le GELA a souscrit une assurance responsabilité civile pour cette étude.

Cet essai est financé par des fonds publics provenant du Ministère de la santé (Programme Hospitalier de Recherche Clinique 2001 N/Ref AOMO 1066) et une aide complémentaire de soutien à la recherche clinique accordée par le laboratoire Chugai Pharma France.

La participation de votre enfant ne peut qu’être volontaire, aussi nous vous demandons si vous y consentez de signer le formulaire de consentement écrit selon les exigences légales.

*Le médecin responsable*
Formulaire de consentement éclairé pour les parents d’un patient mineur

Nous, Monsieur ……………………………………… et Madame ………………………………………
Demeurant à ………………………………………………………………………………………
Certifions que le Docteur ………………… …………………….. nous a proposé de faire participer
notre enfant ……………………………………. à une recherche intitulée «Essai prospectif
randomisé dans les stades III-IV de la maladie de Hodgkin : Evaluation comparative de
l’efficacité et de la toxicité de deux modalités de chimiothérapie, l’ABVD et le BEACOPP »

Le médecin nous a précisé que nous sommes libres d’accepter ou de refuser la participation de
notre enfant à cette recherche et que cela ne changera pas nos relations pour le traitement de
notre enfant.
Afin d’éclairer notre décision, nous avons reçu et bien compris les informations suivantes qui
nous ont été données par écrit et oralement. Le médecin de notre enfant nous a expliqué la
maladie de notre enfant, son stade actuel et les différents traitements indiqués, leurs avantages
et leurs inconvénients respectifs. L’étude proposée vise à comparer l’efficacité et les effets
secondaires du traitement par chimiothérapie habituel (ABVD) à un traitement plus intensif
(BEACOPP) dans la maladie de notre enfant. Ces deux traitements médicaux sont administrés
selon deux schémas différents pendant 6 à 8 mois. Le traitement plus intensif pourrait être
associé à des effets secondaires plus importants que le traitement habituel, mais il pourrait
aussi être plus efficace. La supériorité d’un traitement sur l’autre ne pourra être évaluée qu’au
terme de cette étude. Notre enfant sera régulièrement suivi pendant cette étude et nous avons
pris connaissance des visites et examens médicaux nécessaires au bon déroulement de cette
étude.

Cette recherche a reçu l’avis favorable du Comité Consultatif de Protection des Personnes
participant à une recherche Biomédicale de Créteil Henri Mondor, le --/--/--.

Le promoteur de cette recherche, le Groupe d’Etude des Lymphomes de l’Adulte (GELA) a
contracté une assurance (Société GERLING, 111 rue de Longchamp, 75116 Paris ; N°
2002134 conformément à la loi du 20 décembre 1988 modifiée (Livre IIBis du Code de la Santé
Publique)

Nous acceptons que les données nominatives concernant notre enfant recueillies à l’occasion
de cette recherche puissent faire l’objet d’un traitement automatisé par les organisateurs de la
recherche.

Le droit d’accès et de rectification prévu par la loi « Informatique et Libertés » (Loi du 6 janvier
1978 modifiée le 1er juillet 1994 - article 40-4) s’exerce à tout moment auprès des responsables
de la recherche. Pour toutes les informations de nature médicale, nous exercerons ce droit par
l’intermédiaire d’un médecin de mon choix.

Les données recueillies demeureront strictement confidentielles. Nous n’autorisons leur
consultation que par l’équipe médicale, les personnes dûment mandatées par le promoteur de
la recherche et éventuellement par des représentants des autorités administratives de Santé,
tous soumis au secret professionnel (article 40-3 même loi)

Nous pourrons à tout moment demander toute information complémentaire au Dr (NOM
PRENOM)……………………………………………………(ADRESSE)………………………………
………………………………………………………….….(N°TELEPHONE)………………………………
(E-MAIL…) ………………………….

Version 2.2 99 / 161 23 September, 2004
NOTRE ENFANT .................................. AYANT EXPRIME SON ACCORD, NOUS ACCENTONS LIBREMENT ET VOLONTAIREMENT QU'IL PARTICIPE A CETTE ETUDE MEDICALE DANS LES CONDITIONS DECRITES CI-DESSUS.

Notre consentement ne décharge en rien l’investigateur et le promoteur de leurs responsabilités et nous conservons tous nos droits garantis par la loi.

Nous sommes conscients que nous pouvons retirer notre consentement à tout moment, quelles que soient nos raisons. Le fait que notre enfant ne participe plus à cette recherche ne portera pas atteinte à nos relations avec le médecin investigateur qui continuera à soigner notre enfant dans les meilleures conditions suivant les moyens habituels et ne nous privera pas de nos droits.

Nous gardons un exemplaire de la feuille d’information que nous a remise le Dr (NOM PRENOM) .............................................. et du présent consentement

Fait à , le
NOM PRENOM ET SIGNATURE des deux titulaires de l’exercice de l’autorité parentale :

Signature du père Signature de la mère

Signature de l’enfant

Je, soussigné Dr (NOM PRENOM) ................................. certifie que Monsieur (NOM PRENOM) ................................. Et Madame (NOM PRENOM) ................................. ont donné ce jour leur consentement informé, libre et révocable
à la recherche nommée ci-dessus.

Le Signature :
Appendix H: Information for NCIC CTG Participants

EORTC protocol 20012 / NCIC CTG HD 8

This protocol is coordinated by EORTC and follows the standard EORTC sequence of chapters. The chapters 1-14 and 23 of the protocol are common to both EORTC and NCIC CTG (including the Quality of life and excluding the Health Economics). All scientific, practical and administrative aspects of the protocol specific to NCIC CTG are included under this Appendix and instead of chapters 15-22 (except specified otherwise).

1. NCIC CTG Study Chair
   Dr. Ralph Meyer
   Hematologic Oncologist
   Hamilton Regional Cancer Centre
   699 Concession Street
   Hamilton, Ontario
   L8V 5C2
   Phone: 905-575-7820
   Fax: 905-575-6340
   E-mail: ralph.meyer@hrcc.on.ca

1.1. NCIC CTG Central Office Contact
   Ms. Suzan Moase
   NCIC CLINICAL TRIALS GROUP – QUEEN’s UNIVERSITY
   10 Stuart Street
   KINGSTON ONTARIO K7L 3N6
   Canada
   Phone: +1 613 533 6430
   Fax: +1 613 533 2941
   E-mail: smoase@ctg.queensu.ca

   Dr. Lois Shepherd
   Physician Coordinator
   NCIC Clinical Trials Group
   82-84 Barrie Street, Queen’s University
   Phone: 613-533-6430
   Fax: 613-533-2941
   E-mail: lshepherd@ctg.queensu.ca
2. Chapter 15: NCIC CTG Investigator Authorization Procedure

All investigators (principal and additional investigators) must have on file with the NCIC CTG a current curriculum vitae (updated within the past 2 years). In addition, all principal investigators must have on file with the NCIC CTG a Health Canada “Qualified Investigator Undertaking”.

Each time an institution is locally activated, NCIC CTG will inform the EORTC data manager by faxing a copy of the local activation letter. The local activation letter will serve to inform EORTC that the institution has submitted all documents required for local activation. NCIC CTG will also fax to the EORTC Data Manager the participant’s list which includes the full address and contact information for the investigator and the institution and a copy of the normal lab values of the institution. EORTC will confirm receipt of this documentation and will send confirmation to NCIC CTG that the institution has been added to the authorization list for randomisation.

3. Chapter 16: NCIC CTG Patient Randomisation Procedure

Randomisations for all NCIC CTG institutions will be done through the NCIC CTG Central Office.

Randomisations will be accepted on Monday to Friday between 8:00 AM and 6:00 PM Eastern Time. The eligibility checklist must be completed prior to randomisation (eligibility requirements are listed in Section 3.1. The randomisation may be done by telephone (613-533-6430) or by fax (613-533-2812). As soon as eligibility is ascertained, EORTC will be contacted by the NCIC CTG to obtain the treatment assignment. The NCIC CTG will then relay the treatment assignment to the centre and confirm it in writing.

4. Chapter 17: NCIC CTG Forms and Procedures for Collecting Data

EORTC Case Report Forms (CRFs), with the header modified by the NCIC CTG for their use, will be used by all NCIC CTG institutions.

A single set of case report forms (CRFs) will be sent to each centre (for photocopying and use) following local activation. CRFs should be completed and submitted to the NCIC CTG Central Office (see Section 1 for mailing address) according to the submission schedule in Section 17.1. In addition to the required forms as listed, a copy of the signed consent form must be submitted for each patient. The EORTC and NCIC CTG patient numbers as well as patient initials must be recorded on each form. CRFs will be forwarded to the EORTC by the NCIC CTG. Do not send the forms directly to the EORTC.

Extensive consistency checks on the CRF’s will be carried out at the EORTC Data Center and query forms in case of inconsistent data will be issued by the EORTC Data Manager and sent to the NCIC CTG. Those Query Forms will be forwarded to the centers and must be immediately answered and signed by the investigator (or an authorized staff member). The original must be returned to the NCIC CTG and a copy must be appended to the investigator’s copy of the CRFs. The NCIC CTG will then forward the answered Query Forms to the EORTC Data Manager.
5. **Chapter 18: Reporting Serious Adverse Events (NCIC CTG)**

Adverse event reporting should be based on the Common Toxicity Criteria (CTC) Version 2.0.

NCIC CTG investigators are to report all serious adverse events as described in Section 18.

Serious adverse events (SAEs) must be reported on the EORTC Serious Adverse Event Form (Form 89) and reported by telephone (613-533-6430) and/or fax (613-533-2812) within 24 hours of the event. NCIC CTG will in turn fax all SAE reports to the EORTC Safety Desk within 24 hours of receipt. Any second malignancies or myeloid dysplasia must be reported in writing on an EORTC Serious Event Form (Form 89) within 15 working days of when the diagnosis is known to the investigator.

The NCIC CTG will report all regulatory reportable serious adverse events to the Therapeutic Products Directorate of Health Canada.

6. **Chapter 19: NCIC CTG Quality Assurance**

6.1 **Control of data consistency**

NCIC CTG follows the “standard mailbox” system (see forms and procedures for collecting data). Therefore, data forms will not be entered in the database of the NCIC CTG Central Office and the NCIC CTG Central Office will not perform any consistency checks on the CRF’s.

6.2 **On site quality control** NCIC CTG site monitoring may be conducted at active participating centres at least once every three years in the course of the study. The auditors will require access to patient medical records to verify the data.

No modifications will be done to the CRFs during these procedures.

6.3 **Central Pathology Review**

Patients registered on this study will be asked for their consent to participate in Tissue Banking. Central pathology review will be mandatory for all NCIC CTG centres. At randomization, NCIC CTG will request submission of pathology materials as described in section 19.2 of the protocol. Further information will follow with the NCIC CTG letter of Central Activation.

**Central pathology reviewer:**

Dr. David Dexter  
Kingston General Hospital  
Department of Pathology  
Douglas 2  
76 Stuart Street  
Kingston, Ontario  
K7L 2V7  
E-mail: dexter@cliff.path.queensu.ca
6.4 Other quality controls
The EORTC will perform the data timelines every 3 month. NCIC CTG Central Office will receive the overdue tables and will forward them to the attention of the Principal Clinical Research Associate at the institution.

7. Chapter 20: Ethical Considerations (NCIC CTG)
See Section 20 of the protocol.

This study will be conducted under a Clinical Trial Application (CTA), formerly called an Investigational New Drug (IND) application, in Canada. The principal investigator will ensure this study is conducted in compliance with the protocol, NCIC CTG requirements, ICH-Good Clinical Practice Guidelines and Division 5 of the Canada Food and Drug Regulations.

The following documentation must be on file at the NCIC CTG central office prior to randomization (also see Section 2 for documentation required for investigators):
Required documentation is as follows:

1. Written documentation of full board research ethics board (REB) approval of the protocol and sample consent form. Please note that if the approval letter or form from the REB does not clearly indicate a ‘full board’ review of the initial protocol and consent form was done then either a revised letter/form of approval or the minutes of the REB meeting evidencing a full board review must be submitted.

   If an REB refuses to approve this protocol (or an amendment/revision to this protocol) the NCIC CTG must be notified immediately of the date of refusal and the reason(s).

2. A completed Health Canada ‘Research Ethics Board Attestation’ form (copy attached). If an REB prefers to it may include the following language in the protocol specific REB approval letter/form (signed by the REB chair) instead of completing the Health Canada form:
   ♦ The membership of this Research Ethics Board complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Canadian Food and Drug Regulations
   ♦ This Research Ethics Board carries out its functions in a manner consistent with Good Clinical Practice and
   ♦ This Research Ethics Board has reviewed and approved the clinical trial protocol and informed consent for the trial which is to be conducted by the qualified (i.e. principal) investigator at the specified clinical trial site. This approval and the views of this Research Ethics Board have been documented in writing.

   The REB membership requirements are specified in Section C.05.001 of the regulations.

3. Written documentation confirming the etoposide product monograph was forwarded to the REB.
4. Completed ‘Confirmation of Initial Ethical Approval’ form (copy attached) confirming the protocol was approved by a properly constituted Research Ethics Board and that only REB members independent of the investigator(s) conducting the study participated in deliberations or voting concerning the approval of the study.

5. Copy of the REB approved consent form on institutional letterhead.

A sample consent form is provided. It may be modified to meet local needs as long as the necessary elements are retained. These include a description of the purpose of the study, potential side effects, potential benefits, study design, voluntary participation and confidentiality. The consent form must also contain statements giving permission for medical/study reports concerning the patient to be sent to the NCIC CTG and other sponsoring and monitoring agencies, and for representatives of the NCIC CTG and these agencies to inspect medical/study reports on-site.

Since this study is conducted under a CTA all ICH-GCP elements as listed in section 4.8.10 of the ICH-Good Clinical Practice Guideline must be included in the consent form. If your centre does plan to modify the sample consent please ensure no ICH-GCP elements are eliminated in the modification process.

To avoid delays in your centre's "local" activation, you might wish to send in to the central office your proposed modified consent as soon as it is prepared, rather than wait until after your REB has approved the study. Time permitting, there may then be an opportunity for central office review of the consent to take place and any necessary changes requested before the REB approval process is complete.

A French translation of the sample consent is available on request.

6. Current laboratory accreditation and normal values if not already on file at the NCIC CTG.

7. Completed NCIC CTG Participant's List. A blank participant’s list is enclosed.

This protocol must undergo REB approval at least once per year. This approval may be full board or expedited, according to the policy of your local REB and must continue as long as patients are being accrued or any patients at your centre are undergoing protocol mandated treatments or interventions. Documentation of required REB annual re-approvals must be forwarded to the central office.

8. Chapter 21: Administrative Responsibilities (NCIC CTG)

Administrative responsibilities of EORTC as Coordinating Group are described in chapter 19 of the main protocol.

The NCIC CTG is responsible for handling investigator authorization procedure, for randomization of patients through EORTC Randomisation Desk and will act as a "mail box" in this trial (see forms
and procedures for collecting data). All methodological questions should be addressed to the NCIC CTG who will then forward these questions to the EORTC Data Manager. The NCIC CTG Central Office contact is Ms. Cathy Sears as specified in Appendix 1.1.

9. Chapter 22: Trial Sponsorship and Financing (NCIC CTG)
The NCIC CTG is the sponsor for this study in Canada.

10. Chapter 23: Trial Insurance (NCIC CTG)
Not applicable

11. Drug Supply (NCIC CTG)
Details regarding drug supply for the trial will be specified in a separate letter and distributed to all participating centres.

12. Health economics
NCIC CTG will not participate in the economic evaluation.

12. PATIENT INFORMATION SHEET AND INFORMED CONSENT (NCIC CTG)
Please refer to the NCIC CTG Website to download a current version of the sample consent form. The address is:

www.ctg.queensu.ca
Appendix I: Nordic Lymphoma Group Specific Appendix to the EORTC protocol 20012.

Nordic Lymphoma Group protocol number 20012

This protocol is coordinated by EORTC and follows the standard EORTC sequence of chapters. The chapters 1-14 and 23 of the main protocol are common to all the Nordic Lymphoma Groups participants. All scientific, practical and administrative aspects of the protocol specific to the Nordic Lymphoma Group are included under the Nordic Lymphoma Group Appendix instead of chapters 15-22 (except specified otherwise in the following appendix).

Main contact addresses

**Nordic Lymphoma Group Study coordinator:**
Professor Bengt Glimelius  
Dept of Oncology, Radiology and Clinical Immunology, Section of Oncology,  
University Hospital, SE-751 85 Uppsala, Sweden  
Phone: +46 18 611 55 13  
Fax: +46 18 611 10 27  
E-mail: bengt.glimelius@onkologi.uu.se

**Nordic Lymphoma Group Clinical Trial Office:**
Data Center  
Regional Oncological Centre, University Hospital, SE-751 85 Uppsala, Sweden  
Phone: +46 18 15 19 10  
Fax: +46 18 71 14 45  
e-mail: jonas.nilsson@roc.uas.lul.se
1 Trial organization

This trial is a Nordic Lymphoma Group Trial, jointly conducted by EORTC and Nordic Lymphoma Group.

♦ The EORTC is the coordinating Group in this Intergroup trial and therefore is responsible for the trial design and activation, data management (including the quality control of data), statistical analysis and publication.

♦ Nordic Lymphoma Group will use the protocol developed by EORTC. The present Nordic Lymphoma Group specific Appendix details the participation of all Nordic Lymphoma Group members and therefore it supersede entirely or partially the corresponding chapters (15 – 22) in the main protocol.

♦ The Nordic Lymphoma Group is collaborating group in this trial.

♦ Nordic Lymphoma Group is the legal sponsor for all members of the Nordic Lymphoma Group. Only the Nordic Lymphoma Group can authorize these investigators to randomize patients.

♦ All investigators members of the Nordic Lymphoma Group will call the EORTC Data Center to randomize patients.

♦ Nordic Lymphoma Group will use the standard EORTC SAE definition and the standard EORTC SAE forms.

♦ The Nordic Lymphoma Group Data Center will follow a “standard mail-box” procedure for this trial:
  ♦ Only the EORTC Data Center will code the data, perform consistency checks on data and modify them. Only the EORTC Data Center will do the analysis.
  ♦ There will be no direct communication between investigators members of the Nordic Lymphoma Group and the EORTC Data Center, except for randomization.
  ♦ This trial is an academic trial with an educational grant from the industry to the EORTC Data Center. The Nordic Lymphoma Group will likewise try to raise money for the Nordic Data Center.

2 Scientific matters considered as Group specific and not detailed in the protocol.

No group specific activities will take place. The Nordic group will not participate in the health economic analyses (chapter 11 in the main protocol).

3 Investigator authorization procedure

All regulatory procedures must be completed in cooperation with the Nordic Lymphoma Group Data Center before the investigators can be authorized to register patients in this trial.

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the Nordic Lymphoma Group ’s Data Center:

♦ Commitment form
♦ Ethic Committees approval and a copy of the final patient information sheet
♦ Approval from the Drug authorities in the country.
Signed CV of the local investigator.

- List of staff members, signed by the staff members and the local investigator.
- List of normal laboratory ranges.

Each time an institution has become authorized to enter patients in this trial, the Nordic Lymphoma Group Data Center will inform the EORTC Data Center. The EORTC Data Center will provide immediately the Nordic Lymphoma Group's Data Center with the EORTC institution number for the concerned investigator.

Patient registration/randomization from centers not (yet) authorized will not be accepted.

## 4 Patient randomization procedure

Patient registration will only be accepted from authorized investigators (see "Authorization procedure").

An exhaustive list of questions to be answered during the randomization procedure is included in the Registration Checklist. The responsible investigator should complete The Registration Checklist and all the baseline forms before the patient is randomized.

All investigators members of the Nordic Lymphoma Group can randomize patients at the EORTC Data Center as described in the chapter 16 of the main protocol. Randomization can then either be done through the INTERNET network (http://www.eortc.be/random) 24 hours a day, 7 days a week or by telephone from 9.00 am to 5.00 pm (Belgian local time), Monday through Friday (Tel: +32 2 774 16 00).

Alternatively, for those centers who wish not to randomize themselves, the randomization checklist could be sent to the Nordic Lymphoma Group's Data Center by fax:

**Fax number +46 18 71 14 45**

**Contact the Data Center by phone +46 18 15 19 40 if problems arise.**

As soon as this form is received, the Nordic Lymphoma Group's Data Center will randomize (09.00 – 16.00 Monday to Friday) the patients at the EORTC Data Center as described in the chapter 16 of the main protocol.

**Contact person: Karin Hellström**

During the randomization the information on the group affiliation will be collected:

**Primary Group affiliation:** for all the investigators participating on behalf of the Nordic Lymphoma Group, the primary Group affiliation is Nordic Lymphoma Group, “NLG”.

Secondary Group affiliation:

- for the Investigators members of both the Nordic Lymphoma Group and the EORTC Lymphoma Group, the secondary affiliation should be completed "EORTC" if they wish their patients to be counted also for the EORTC membership .

At the end of this procedure, the sequential identification number and the treatment will be allocated to the patient. The Investigator/Staff member contacting the EORTC Data Center and the Nordic Lymphoma Group Data Center will receive this information (The NLG by an automatic E-mail). If the Nordic Lymphoma Group Data Center is performing the randomization, it will forward the information immediately to the investigators.

This sequential identification number of patient has to be recorded on all the forms. All the forms should then be sent to the Nordic Lymphoma Group's Data Center, which will send it to the EORTC Data Center.
5 Procedures for collecting data

The data will be reported on the EORTC forms. However, these forms will be adapted to include some Nordic Lymphoma Group specific administrative information in the header.

All the Investigators participating on behalf of Nordic Lymphoma Group will send all the forms to:

Nordic Lymphoma Group Data Center  
Regional Oncological Centre  
University Hospital  
SE-751 85 Uppsala  
Sweden

The Nordic Lymphoma Group's Data Center will follow a “mail-box” procedure for this trial.

This means that:

♦ Signed original CRFs will be collected by the Nordic Lymphoma Group Data Center and sent regularly to the EORTC Data Center according to the form flow schedule (provided with the CRFs)
♦ Investigators will not be allowed to send CRFs directly to the EORTC Data Center
♦ The Nordic Lymphoma Group's Data Center will not modify the forms nor enter them into the computer
♦ The EORTC Data Center will enter the data in the computer for quality control and analysis. When necessary, queries will be transmitted to the Nordic Lymphoma Group's Data Center, which will send them to the investigators. The Nordic Lymphoma Group's Data Center will then send the reply of the investigators back to the EORTC Data Center.

6 Reporting adverse events

The Nordic Lymphoma Group defines adverse events (AEs), serious adverse events (SAEs), adverse drug reactions (ADRs) as in the main protocol, paragraph 18.1.

Death due to progression of disease and hospitalization because of planned treatment or other protocol specified activities like response evaluations will not be considered as an SAE and therefore not reported as an SAE.

♦ All AE and ADR must be recorded as indicated in the protocol.
♦ All SAEs occurring during the treatment period and within 30 days after the last protocol treatment administration must be reported to the Nordic Data Center by fax within 24 hours of the initial observation of the event:

  Nordic Lymphoma Group Data Center  
  Fax no +46 18 71 14 45

♦ The complete report needs to be sent within 10 days
Nordic Lymphoma group Data Center will fax all SAEs within 24 hours after that they have been recorded at the data center to the EORTC safety desk:

EORTC Safety Desk
fax no +32 2 772 8027

The Nordic Data Center will during the day the fax is recorded evaluate whether the SAE must be reported to the drug authorities or whether it will be forwarded only to the EORTC safety desk. Thus, the data center, with help of the study coordinator of the Nordic Lymphoma Group will evaluate whether the SAE is unexpected and likely related to the allocated treatment, requiring further actions. Whether this is done or not will be informed to the EORTC Data Center.

The EORTC forms will be used.

7 Quality assurance

No immediate quality assurance activities will be performed after authorization of a particular center. If help is needed in understanding the procedures, the CRFs and how they are completed, this will be provided by the regional investigators (see the short protocol, version) or the coordinator in Sweden, prof Bengt Glimelius.

7.1 Control of data consistency

Nordic Lymphoma Group follows the "standard mailbox" system (see forms and procedures for collecting data).

Therefore, data forms will not be entered in the database of the Nordic Lymphoma Group Data Center and the Nordic Lymphoma Group's Data Center will not perform any consistency checks on the CRFs.

7.2 On-site quality control

The Nordic Lymphoma Group will register all incoming CRFs from the investigators and all queries from the EORTC Data Center. The only quality control that automatically will be performed is that the patient has been randomized and included in the trial. In the case a certain center receives several queries, a control will be made of the CRFs to avoid that too many mistakes are included in the CRFs sent to the EORTC Data Center.

No modifications will be done to the CRFs during these procedures. It is important that the EORTC Data Center identifies problematic Nordic centers so that they can receive help.

7.3 External review of histology

According to the protocol (19:2), the local pathologist must send either fifteen (15) unstained slices or paraffin blocks together with the original pathology form to the Nordic Data Center. The including doctor must immediately inform the local pathologist that this has to be done within two weeks. The Nordic Lymphoma Group Data Center will forward the material to the Panel Committee address (see main protocol).

7.4 Other quality controls

The EORTC will perform the data timelines every 3 month. Nordic Lymphoma Group Data Center will receive the overdue tables. This information will be sent to all participating centers within 10 days.
8 Ethical considerations
The Nordic Lymphoma Group will adapt the Ethical considerations in the main protocol (paragraph 20). Before any center is authorized to include patients, a copy of the approval must be sent to the NLG Data Center.

9 Administrative responsibilities

9.1 The study coordinator
The Study Coordinator of Nordic Lymphoma Group will be responsible for the function of the Nordic Data Center, the authorization of individual centers in Sweden and in the other Nordic countries after information by the National study coordinators, discussion of all unclear SAEs and be of help in resolving all unclear issues in the contacts between Nordic group centers and the EORTC Data Center.

NLG Study coordinator:
Professor Bengt Glimelius
Dept of Oncology, Radiology and Clinical Immunology, Section of Oncology, University Hospital, SE-751 85 Uppsala, Sweden
Phone: + 46 18 611 55 13
Fax: +46 18 611 10 27
E-mail: bengt.glimelius@onkologi.uu.se

The national coordinators are:

Overlæge Mads Hansen
Hæm. afd. L 4042 Finsencentret,
H:S Rigshospitalet Blegdamsvej 9
2100 København Ø
Phone: +45 35451128
Email: mth@daldnet.dk

Dr Taina Turpeenniemi-Hujanen
Dept. Oncology and Radiotherapy
Oulu University Hospital, Oulu, Finland
Phone: (358) 8 315 6445
Fax (358) 8 315 6449
Email: turpeenniemi.hujanen@ppshp.fi
9.2 The Data Center

The Nordic Lymphoma Group Data Center is responsible for handling investigator authorization procedure, for help with randomization of patients from centers that will not do randomization themselves, and will act as a "mail box" in this trial (see forms and procedures for collecting data). All methodological questions should be addressed to the Nordic Lymphoma Group Data Center that will address them to the person competent for this trial.

The Nordic Lymphoma Group Data Center is responsible for all the administrative procedures required for the trial following the normal procedures of Nordic Lymphoma Group and respecting the present appendix.

The data center is also responsible, as an intermediate, to guarantee the fluent communication between the EORTC Data Center and the Investigators participating on behalf of the Nordic Lymphoma Group.

Nordic Lymphoma Group Data Center
Regional Oncological Center
University Hospital
SE-751 85 Uppsala
Sweden

Statistician:
Jonas Nilsson
Regional Oncological Center
University Hospital
SE-751 85 Uppsala
Sweden
Tel: +46 18 15 19 19
E-mail: jonas.nilsson@roc.uas.lul.se

Data Manager:
Karin Hellström
Regional Oncological Center
University Hospital
SE-751 85 Uppsala
Sweden
Tel.: +46 18 15 19 30
E-mail: karin.hellstrom@roc.uas.lul.se
Medical Advisor:
Professor Bengt Glimelius
Dept of Oncology, Radiology and Clinical Immunology, Section of Oncology, University Hospital, SE-751 85 Uppsala, Sweden
Phone: + 46 18 611 55 13
Fax: +46 18 611 10 27
E-mail: bengt.glimelius@onkologi.uu.se

9.3 The NORDIC LYMPHOMA GROUP

Nordic Lymphoma Group is responsible as a Nordic Lymphoma Group to guarantee the general compliance of their members to procedures described in this appendix.

All questions concerning membership in the Nordic Lymphoma Group should be addressed to the chairman of the Nordic Lymphoma Group.

Chairman:
Christian Geisler
Dept. Hematology 4042
Rigshospitalet, DK 2100 Copenhagen, Denmark
Phone: (45) 35 45 11 46
Fax (45) 35 34 48 41
Email: geisler@rh.dk

10 Trial sponsorship and financing

Nordic Lymphoma Group is a Legal Sponsor for all investigators participating on behalf of the Nordic Lymphoma Group. The Group will try to get funding from the Nordic Cancer Union and will seek educational grants from Industry.

11 Trial Insurance for the Nordic Lymphoma Group

No special insurance required since the patients are covered by the regular health care systems in the four Nordic countries.

11 Patient information sheet and informed consent

This sheet has been approved for centers in Sweden (see 12 A).
The sheets that will be approved in the other Nordic countries will be added.
Appendix J: GELCAB Group Specific Appendix.

EORTC Protocol 20012
Administrative Appendix

This protocol is coordinated by EORTC and follows the standard EORTC sequence of chapters. The chapters 1-14 of the protocol are common to all the groups. All scientific, practical and administrative aspects of the protocol specific to GELCAB are included under the GELCAB Appendix of the protocol and instead of chapters 15-23 (except specified otherwise in the following appendix).

Contact addresses (GELCAB GROUP)

GELCAB study coordinator: Dr. Anna Sureda, MD. Clinical Hematology Division. Hospital de la Santa Creu i Sant Pau. Antoni Maria i Claret, 167. 08025 Barcelona, Spain
Phone: + 34 93 2919396
Fax: + 34 93 2919466
E-mail: asureda@hsp.santpau.es

GELCAB clinical trial office: Clinical Hematology Division. Hospital de la Santa Creu i Sant Pau. Antoni Maria i Claret, 167. 08025 Barcelona, Spain. Tel: +34 93 2919396, Fax: + 34 93 2919466. E-mail: ccanals@hsp.santpau.es

Data Manager
Esther Soler
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Fax: + 34 93 2919466
e-mail: esoler@hsp.santpau.es

Statistician
Dr. Albert Altés, MD
Phone: + 34 93 2919396
Fax: + 34 93 2919466
e-mail: aaltesh@hsp.santpau.es
1 Trial organization

This trial is an Intergroup Trial, jointly conducted by EORTC and GELCAB.

♦ The EORTC is the coordinating group in this Intergroup trial and therefore is responsible for the trial design and activation, data management (including the quality control of data), statistical analysis and publication.

♦ The protocol developed by EORTC will be used by GELCAB. The present GELCAB Group specific Appendix details the participation of all GELCAB institutions in the trial. The content of this appendix is therefore applicable only to GELCAB investigators, for whom they supercede entirely or partially the corresponding chapters in the protocol.

♦ The GELCAB is a collaborating group in this trial.

♦ GELCAB is the legal sponsor for all GELCAB participants.

♦ All GELCAB investigators will call the GELCAB Data Center to randomize patients.

♦ GELCAB will use the standard EORTC SAE definition and the standard EORTC SAE forms.

♦ The GELCAB Data Center will follow a “standard mail-box” procedure for this trial:

♦ Only the EORTC Data Center will code the data, perform consistency checks on data and modify them. Only the EORTC Data Center will do the analysis.

♦ There will be no direct communication between GELCAB investigators and the EORTC Data Center.

2 Investigator authorization procedure

All regulatory procedures must be completed in cooperation with the GELCAB Data Center before the investigators can be authorized to register patients in this trial.

Each time an institution has become authorized to enter patients in this trial, the GELCAB Data Center will inform the EORTC Data Center. The EORTC Data Center will provide immediately the GELCAB Data Center with the EORTC institution number for the concerned investigator.

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the GELCAB Data Center:

♦ a commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,

♦ a signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared by the commitment form.

♦ a copy of the letter of acceptance of the protocol by their local ethics committee,

♦ the list of their staff members authorized to sign case report forms, with a sample of each authorized signature.

and, if the following documents are not yet available at the GELCAB Data Center:

♦ their updated Curriculum Vitae,

♦ the list of the normal ranges, in their own institution, of all laboratory data required by the protocol,
The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

♦ all the above mentioned documents are available at the GELCAB Data Center
♦ all applicable national health authorities requirements are fulfilled

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

3 Patient randomization procedure

Patient registration will only be accepted from authorized investigators (see "Authorization procedure").

An exhaustive list of questions to be answered during the randomization procedure is included in the EORTC Registration Checklist. The responsible investigator should complete the EORTC Registration Checklist and all the baseline forms before the patient is randomized.

All GELCAB Investigators should send the randomization checklist to the GELCAB Data Center by fax.

Esther Soler
Fax +34 93 2919466

As soon as this form is received, the GELCAB Data Center will randomize the patients at the EORTC Data Center.

The GELCAB Data Center will randomize patients as described in the chapter 16 of the main protocol.

At the end of this procedure, the sequential identification number and the treatment will be allocated to the patient. The GELCAB Data Center will receive this information by an automatic E-mail and will forward it immediately to the investigators.

This sequential identification number of patient has to be recorded on all the forms. All the forms should be then sent to the GELCAB Data Center, which will send it to the EORTC Data Center.

4 Procedures for collecting data

All the Investigators participating on behalf of GELCAB will send all the forms to:

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Clinical Hematology Division.
Hospital de la Santa Creu i Sant Pau.
Antoni Maria i Claret, 167
08025 Barcelona, Spain.
Tel: +34 93 2919396
Fax: +34 93 2919466
E-mail: esoler@hsp.santpau.es

The GELCAB Data Center will follow a “mail-box” procedure for this trial.
This means that:

♦ Signed original CRFs will be collected by the GELCAB Data Center and sent regularly to the EORTC Data Center according to the form flow schedule (provided with the CRFs)
♦ Investigators will not be allowed to send CRFs directly to the EORTC Data Center
♦ The GELCAB Data Center will not modify the forms nor enter them into the computer
♦ The EORTC Data Center will enter the data in the computer for quality control and analysis. When necessary, queries will be transmitted to the GELCAB Data Center, which will send them to the investigators. The GELCAB Data Center will then send the reply of the investigators back to the EORTC Data Center.

Concerning the GELCAB investigators, if any procedure is not followed as requested or if any quality remark should be formulated, this will be addressed first to the GELCAB Data Center.

Inversely, if the EORTC has any general comments on the compliance of GELCAB investigators to the protocol, this will be addressed to the GELCAB Data Center.

5 Reporting adverse events

Adverse event reporting should be based on the common toxicity criteria (CTC) Version 2.0.

GELCAB investigators are to report all serious adverse event as described in section 18 of the main protocol.

Serious adverse events (SAE’s) must be completed on the English EORTC form (SAE form 89) and reported to the GELCAB Data Center by telephone or fax (+ 34 93 2919466) within 24 hours of the event. GELCAB will fax all SAE’s to the EORTC Safety Desk (fax: +32 2 772 80 27) within 24 hours of receipt.

GELCAB will report all regulatory reportable SAE’s to “the ministry of Health” in Spain

6 Quality assurance

6.1 Control of data consistency

GELCAB follows the “standard mailbox” system (see forms and procedures for collecting data).

Therefore, data forms will not be entered in the database of the GELCAB Data Center and the GELCAB Data Center will not perform any consistency checks on the CRFs.

6.2 External review of histology

A centralized pathology review is included in this trial.

Within two weeks from the date of registration, the local pathologist must send to the central pathology reviewer the following material:

♦ ten(10) unstained slides or paraffin blocks(s)
♦ the original pathology form (only the local pathology part should be completed)
Central pathology reviewer:
   Ramón Bordes, MD
   Servicio de Anatomía Patológica
   Hospital de la Santa Creu i Sant Pau
   Antoni Maria i Claret, 167
   08025 Barcelona, Spain
   Phone number 34-93-2919346
   Fax number 34-93-2919344
   e-mail rbordes@hsp.santpau.es

The final diagnosis of the central pathologist will be considered as definitive for the trial.
The diagnosis made by the local pathologist of the participating center will be accepted for the registration.

6.3 Other quality controls
The EORTC will perform the data timelines every 3 months. GELCAB Data Center will receive the overdue tables and will be responsible for the contact with all participating institutions in order to have the missing data completed.
In case of serious overdue data, the principal investigator would take the necessary actions.

7 Ethical considerations

7.1. Patient protection
The responsible investigator will ensure that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments).
The protocol has been written and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical practice (ref: http://www.ifpma.org/pdf/ifpma/e6.pdf).
The protocol will be approved by the Local Ethical Committees as well as by the Spanish Ministry of Health.

7.2. Subject identification
The name of the patient will not be asked for nor recorded at the data Center. A sequential identification number will be automatically attributed to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, patient’s initials (maximum of 4 letters), date of birth and local chart number will also be reported on the case report forms.

7.3. Informed consent
All patients will be informed of the aims of the study, the possible adverse events, the procedures and hazards to which he/she will be exposed, and the mechanism of treatment location. They will be informed as to the strict confidentiality of their patient data, but that authorized individuals other than their treating physician may review their medical records for trial purposes.
The example of the patient informed consent will be translated into Spanish by the individual investigator. The translated version will be dated and the bold sections of the original patient informed consent will appear in the Spanish translated version.

The Spanish informed consent form is part of the documents to be submitted to the ethics committee for approval. The competent ethics committee for each institution will validate local informed consent documents before the center can join the study. Translation will be performed following the Good Clinical Practice guidelines. This also implies that “the written informed consent form will be signed and personally dated by the patient or by the patient’s legally acceptable representative”.

In the informed consent, it will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent will be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This will be done in accordance with the Spanish national and local regulatory requirements.

### 8 Administrative responsibilities

#### 8.1 The study coordinator

The Study Coordinator of GELCAB is member of the steering committee for this protocol.

She will generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

**GELCAB Study coordinator:**

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08025 Barcelona, Spain  
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Fax: + 34 93 2919466  
E-mail: asureda@hsp.santpau.es

#### 8.2 The Data Center

The GELCAB Data Center is responsible for handling investigator authorization procedure, for randomization of patients and will act as a "mail box" in this trial (see forms and procedures for collecting data). All methodological questions should be addressed to the GELCAB Data Center that will address them to the person competent for this trial.

The GELCAB Data Center is responsible for all the administrative procedures required for the trial following the normal procedures of GELCAB and respecting the present appendix.

The data center is also responsible, as an intermediate, to guarantee the fluent communication between the EORTC Data Center and the Investigators participating on behalf of GELCAB.
8.3 The GELCAB

GELCAB is responsible as a group to guarantee the general compliance of their members to procedures described in this appendix.

All questions concerning membership in the group should be addressed to the chairman and/or secretary of the group.

Chairman:
Prof. Emili Montserrat, MD PhD
Address: Hospital Clínic i Provincial. Villarroel, 170. 08036 Barcelona, Spain.
Phone: + 34 93 2279811
Fax: + 34 93 2279811
E-mail: EMONTSE@clinic.ub.es

Secretary: NO SECRETARY

9 Trial sponsorship and financing

GELCAB is the Legal Sponsor for all patients treated within a GELCAB institution.

All GELCAB investigators will be accepted to participate to the trial if all documents required in the chapter 2 of the present appendix were provided.

10 Trial Insurance for GELCAB

GELCAB insurance covers all patients treated within a GELCAB institution.
11 Patient information sheet and informed consent
Formato estándar para un documento de consentimiento informado de la EORTC

Éste es un ensayo clínico.
En un ensayo clínico, sólo se incluyen los pacientes que aceptan participar.
Tómese el tiempo que necesite para tomar su decisión.

Título del protocolo de investigación: Estudio Intergrupo de BEACOPP / ABVD en la Enfermedad de Hodgkin (EORTC protocolo 20012). Estudio aleatorizado fase III del régimen BEACOPP (escalado x 4 ciclos + basal x 4 ciclos) vs. ABVD (x 8 ciclos) en pacientes con estadios III y IV con 3 o más factores de mal pronóstico según el índice pronóstico internacional.

1. Invitación a participar en el estudio
"El Grupo de Linfoomas de la EORTC está iniciando un estudio de investigación en pacientes que tienen una enfermedad similar a la suya. El estudio se llevará a cabo en Europa, Canadá, Australia y Nueva Zelanda bajo la supervisión de médicos reconocidos como expertos en este campo de la medicina. Hoy, se le invitará a participar en este proyecto de investigación después de que haya recibido una información completa acerca del mismo."

2. Introducción

Su enfermedad se llama linfoma de Hodgkin. Afecta a los ganglios linfáticos. En su caso, el estudio de extensión realizado ha demostrado la existencia de lesiones diseminadas.

La evolución espontánea de su enfermedad (cuando no se trata) es desfavorable. Sin embargo, la mayoría de las veces, esta enfermedad se puede curar con los tratamientos disponibles actualmente.

La finalidad de estos tratamientos es conseguir la desaparición de todas las lesiones actualmente visibles, evitar que vuelva a producirse la enfermedad (a corto o a largo plazo) y limitar los riesgos de complicaciones tardías. El valor de los tratamientos existentes en la actualidad se ha demostrado durante muchos años. El tratamiento habitual es una quimioterapia combinada administrada en 8 ciclos secuenciales a lo largo de 8 meses. El régimen quimioterápico estándar actual, llamado "ABVD", combina cuatro fármacos que se utilizan desde hace varios años (doxorrubicina, bleomicina, vinblastina y dacarbacina).

Sin embargo, todavía es posible mejorar sus resultados y reducir su toxicidad. Por lo tanto, es necesario que todos los tratamientos se sometan a evaluaciones comparativas.

Estudios anteriores sugieren que un régimen quimioterápico más intensivo, llamado BEACOPP (bleomicina, etopósido, doxorrubicina, ciclofosfamida, vincristina, procarbacina y prednisona) administrado cada 3 semanas durante 8 ciclos durante 6 meses, puede mejorar el resultado de su enfermedad. Los 4 primeros ciclos se administran a dosis más altas (BEACOPP "escalado") que los 4 últimos ciclos (BEACOPP "basal"). Por lo tanto, este proyecto de investigación clínica, diseñado como ensayo en fase III y en el que participarán aproximadamente 600 pacientes, comparará el tratamiento ABVD estándar con el tratamiento BEACOPP para evaluar cuál de los dos tratamientos puede mejorar los resultados para el paciente.
3. Descripción de la investigación

Para establecer de forma definitiva si alguno de los tratamientos mencionados arriba es mejor, médicos de Europa, Canadá, Australia y Nueva Zelanda tratarán a sus pacientes de acuerdo con este proyecto de investigación clínica. Harán falta unos 5 años para incluir a 600 pacientes y cerca de un año después de incluir al último paciente para analizar los datos y disponer de los resultados. Por lo tanto, para contestar esta pregunta, el azar (se llama "aleatorización" y la realiza un ordenador central) decidirá si será tratado con el régimen ABVD o el régimen BEACOPP. Ni Usted ni su médico pueden decidir qué tratamiento recibirá. Sus posibilidades de recibir ABVD o BEACOPP son el 50% en ambos casos. Se le informará a que brazo de tratamiento ha sido asignado.

El objetivo principal de este estudio es determinar cuál de los tratamientos es más eficaz, menos tóxico y aporta más comodidad al paciente.

En el brazo ABVD, los medicamentos se administran por vía intravenosa dos veces al mes (un ciclo) durante 8 ciclos mensuales.

En el régimen BEACOPP, algunos fármacos (bleomicina, etopósido, doxorubicina, ciclofosfamida y vincristina) se administran por vía intravenosa (tres inyecciones intravenosas durante la primera semana y una inyección intravenosa al principio de la segunda semana para cada ciclo de tres semanas). Procarbacina y prednisona se administran por vía oral.

Para recibir el tratamiento, se le puede ingresar en el hospital o puede recibirlo en la clínica ambulatoria, lo que quiere decir que no tiene que pernoctar en el hospital después de recibir la medicación. Esto dependerá de la organización del hospital y de su capacidad para tolerar el tratamiento.

Antes de iniciar el tratamiento, se realizarán controles médicos. Estos incluyen una exploración física, análisis de sangre (hemogramas, bioquímica sérica, serologías víricas), pruebas radiológicas (incluyendo TAC, gammagrafía y/o ecografía), biopsia de ganglio linfático y biopsia de médula ósea para estudiar una posible afectación de la médula por parte de su enfermedad. En algunos casos, cuando está indicado clínicamente, también se puede extraer un trozo de hígado para examinarlo. Si es necesario, también se medirán niveles de hormonas en su sangre. Se evaluará la función pulmonar y cardíaca. La quimioterapia puede inducir esterilidad en los hombres. Por lo tanto, como precaución, se recomienda congelar su esperma.

Para verificar el diagnóstico inicial (realizado por el anatomopatólogo en su hospital), laminillas de las biopsias tumorales (extraídas en el momento de establecer el diagnóstico) serán revisados por uno o varios anatomopatólogos expertos en el campo y designados por los investigadores principales del estudio para tal fin. La mayoría de veces, los expertos no trabajarán en el hospital donde recibirá el tratamiento bajo este protocolo, ni siquiera en el mismo país. En algunos casos, cuando es difícil establecer/confirmar el diagnóstico, se solicitarán bloques de la pieza anatomopatológica inicial. Este material se utilizará para preparar nuevas laminillas y llevar a cabo investigaciones diagnósticas adicionales.

Antes de cada ciclo de quimioterapia, habrá una exploración física con control del hemograma y de la función pulmonar y cardíaca. Si está indicada clínicamente, se realizará una radiografía del pulmón.

Después de los ciclos 4 y 6, será necesario realizar los procedimientos siguientes: análisis de sangre (hemograma y bioquímica), exploración física, exploración radiológica (TAC) de su tórax, abdomen y pelvis. Si la médula ósea y/o el hígado estaban afectados antes del tratamiento, habrá que volver a examinarlos.

Al final del tratamiento (el tratamiento completo es de 8 ciclos), se llevarán a cabo los siguientes procedimientos: análisis de sangre (hemograma y bioquímica), exploración física, exploración...
radiológica (TAC) de su tórax, abdomen y pelvis. Si la médula ósea y/o el hígado estaban afectados antes del tratamiento, habrá que volver a examinarlos.

Después de finalizar el tratamiento objeto del protocolo, tendrá que volver para visitas de control cada tres meses durante los tres primeros años. En los años 4 y 5, se realizarán controles cada 6 meses y, después de 5 años, se realizarán visitas anuales. En el curso de las visitas, se realizarán los siguientes procedimientos: análisis de sangre (hemograma y bioquímica), exploración física, exploración TAC de su tórax, abdomen y pelvis (esto se realizará a los 6, 12 y 24 meses después de terminar el tratamiento).

A todos los pacientes se les pedirá que rellenen un cuestionario. El cuestionario debe rellenarse antes de iniciar el tratamiento, al final del tratamiento y luego cada año, durante un período máximo de 10 años. En el cuestionario se le harán preguntas a cerca de cómo se siente y tarda unos 10 minutos en rellenarse. Puede recordarle algunos aspectos desagradables de su tratamiento o enfermedad. Algunas de las preguntas son personales y puede negarse a contestarlas si lo desea. La información que aporta es para fines de investigación y será estrictamente confidencial. Las personas (por ejemplo, médicos, enfermeras, etc.) que intervienen directamente en su cuidado normalmente no verán sus respuestas a estas preguntas -- si quiere que sepan esta información, hágaloslo saber.

4. Descripción de los riesgos y molestias previsibles

Los principales efectos adversos de la quimioterapia con ABVD son: pérdida de pelo reversible y cambios transitorios en los recuentos de células sanguíneas (glóbulos blancos y rojos, plaquetas). Un recuento bajo de glóbulos blancos (que son los mecanismos antiinfecciosos de primera línea del cuerpo), llamado neutropenia, durante unos pocos días hace que los pacientes sean vulnerables a infecciones bacterianas.

El fármaco vincristina puede provocar debilidad y hormigueo (en las extremidades) y estreñimiento.

La posible aparición de anemia que induce cansancio, puede justificar la realización de transfusiones de sangre. La quimioterapia también puede inducir esterilidad en los hombres. Las mujeres en edad fértil deben tomar medidas anticonceptivas adecuadas durante el tratamiento. Sin embargo, como medida de precaución, se recomienda la congelación de esperma y ovocitos.

Pueden producirse problemas pulmonares (dificultades respiratorias, tos), en muy raras ocasiones al principio del tratamiento con bleomicina pero a veces más tarde, lo que justifica dejar de fumar y someterse a seguimiento de la función pulmonar.

Pueden producirse problemas cardíacos (dificultades respiratorias, cansarse rápidamente, tos, pies hinchados) en los meses o años que siguen a la administración de adriamicina, lo que también justifica dejar de fumar y someterse a seguimiento de la función cardíaca.

El tratamiento con BEACOPP es más intenso, los efectos adversos pueden ser más intensos que con el tratamiento estándar. Para el primero ciclo de quimioterapia, es posible que se le ofrezca administrarlo como paciente ingresado. Hay que evitar recuentos bajos de glóbulos blancos. Para ello, se utiliza simultáneamente un fármaco (factor de crecimiento, G-CSF) que estimula la producción de glóbulos blancos y, por lo tanto, es capaz de reducir la intensidad y duración de la neutropenia. Para evitar infecciones, es posible que se le ofrezcan antibióticos orales. Pueden haber reacciones alérgicas. Existe un riesgo mayor de infertilidad en los hombres y esterilidad y menopausia precoz en las mujeres de más de 30 años. Como medida de precaución, se recomienda la congelación de esperma y ovocitos. Sin embargo, durante todo el tratamiento, las mujeres en edad fértil deben tomar medidas anticonceptivas adecuadas. Los efectos secundarios cardíacos y
pulmonares son menores comparado con el ABVD. En casos muy raros, efectos tardíos pueden comprometer la producción de células sanguíneas o incluso causar leucemia.

Los efectos secundarios de la quimioterapia serán monitorizados estrechamente y la dosis de los fármacos se ajustará en función del grado de síntomas. En algunos casos, se quitará un fármaco del régimen y posiblemente se sustituirá con otro. En casos muy graves, se interrumpirá el tratamiento objeto del protocolo. El tratamiento posterior se administrará a discreción del investigador y respetando los mejores intereses del paciente.

5. Descripción del objetivo final de la investigación

La propuesta actual es valorar si el tratamiento con BEACOPP puede mejorar el resultado para el paciente comparado con los 8 ciclos del régimen ABVD estándar en pacientes con enfermedad de Hodgkin avanzada. Al mismo tiempo, este estudio de investigación evaluará bajo cuál de los dos tratamientos puede hacer desaparecer por completo la enfermedad y durante cuánto tiempo, si los pacientes viven más tiempo, si puede mejorarse su calidad de vida, si se manifestarán otros tipos de cáncer y cuál de los tratamientos es menos caro.

6. Beneficios esperados (descripción de los posibles beneficios esperados)

Nadie sabe si su participación en este estudio le beneficiará. Su enfermedad puede responder al tratamiento puede sentirse mejor. Puede haber menos posibilidades de recaída y, consiguientemente, la supervivencia a largo plazo puede mejorar.

Su calidad de vida puede mejorar. No es posible predecir estas cosas con certeza para Usted. La información obtenida de este estudio puede ayudar a pacientes con su misma patología en el futuro.

Si su enfermedad empeora, si los efectos secundarios se vuelven graves, si información nueva indica que este tratamiento no está en sus mejores intereses o su médico opina que este tratamiento ya no está en sus mejores intereses, el tratamiento será interrumpido. Se hablará con Usted del tratamiento posterior. Si se descubren durante el estudio efectos secundarios nuevos o información nueva acerca de su enfermedad o tratamiento, se le informará de ello.

7. Participación voluntaria

"Su participación en este ensayo de investigación es totalmente voluntaria y se le dará tiempo suficiente para decidir si desea participar o no. Usted es libre de decidir en todo momento, sin tener que explicar el motivo, que ya no desea participar en el ensayo. El abandono del ensayo no afectará de ningún modo a su tratamiento posterior o su relación con el médico responsable de su tratamiento o con el personal del hospital."

8. Protección de datos

"El ensayo implica la recogida de información contenida en su expediente médico y que está relacionada con su enfermedad. Es muy importante que la información recogida sea precisa y, de tiempo en tiempo, es posible que se coteje con su expediente médico. Personas debidamente autorizadas (personal de la EORTC, representantes de las autoridades sanitarias nacionales y/o extranjeras, o determinadas personas de la empresa que aporta la medicación de estudio) pueden tener acceso a sus datos médicos. Toda la información será estrictamente confidencial y su
identidad no se divulgará nunca. Tiene derecho a acceder a esta información de acuerdo con las leyes aplicables en su país."

"Para verificar el diagnóstico inicial (realizado por el anatomopatólogo en su hospital), laminillas de las biopsias tumorales (extraídas en el momento de establecer el diagnóstico) serán revisados por uno o varios anatomopatólogos, de referencia en el campo. La mayoría de veces, los expertos no trabajaran en el hospital donde recibirá el tratamiento bajo este protocolo, ni siquiera en el mismo país. En algunos casos, cuando es difícil establecer/confirmar el diagnóstico, el anatomopatólogo de referencia pedirá una muestra (congelada) de su biopsia tumoral. Este material se utilizará para preparar nuevas laminillas y llevar a cabo investigaciones diagnósticas adicionales."

"Este ensayo se lleva a cabo con el apoyo de la EORTC y la participación económica restringida de AMGEN."

9. Seguro

El promotor de este estudio es GELCAB. Los participantes en este estudio están cubiertos por un Seguro que cubre los daños y perjuicios que pudieran resultar como consecuencia de su realización. Dicha póliza de seguros cumple lo establecido con la legislación vigente (Ley 25/90 del Medicamento y Real Decreto 561/93).

Si necesita someterse a otro tratamiento médico, le aconsejamos que informe de ello al investigador para asegurar que no tendrá ningún efecto sobre su participación en el ensayo.

Se ha hecho todo lo posible - y se seguirá haciendo - para evitar que sufra cualquier problema de salud adicional como resultado de su participación en este ensayo.

10. Comité Ético

Este protocolo de investigación ha sido sometido al comité ético, cuya misión es verificar el cumplimiento de todas las condiciones con respecto a su seguridad y sus derechos. Esta investigación ha sido aprobada por el Comité Ético de ......................... el ..........................
11. Personas de contacto

En caso de problemas o dudas, su médico tendrá mucho gusto en contestar cualquier otra pregunta que pueda tener. Sus datos son los siguientes:

Nombre del médico: ........................................................
Hospital: ....................................................................
Teléfono: ........................................................................

Si acepta participar en este ensayo, se le dará un número de teléfono en el hospital que podrá llamar a cualquier hora del día si no se siente bien o tiene más preguntas. A su médico de cabecera también se le informará de su participación en este ensayo y lo que comporta, si Usted está de acuerdo.

Tómese el tiempo que necesite para considerar esta información y no dude en hacer más preguntas a su médico si hay algo que no ha quedado claro. Tiene derecho a quedarse con una copia de este documento después de que Usted y su médico lo hayan firmado.
Aceptar la participación

(sí un paciente tiene menos de 18 años, el consentimiento informado debe obtenerse conforme a las normativas nacionales aplicables en el país en que se lleva a cabo el estudio)

☐ He sido informado/a correctamente de la investigación clínica que se me propone
☐ He sido informado/a correctamente de la investigación clínica que se propone al niño
☐ El/la niño/a ha sido informado/a correctamente de la investigación clínica que se le propone
☐ He recibido una copia de la hoja de información para el paciente
☐ He recibido una copia de la hoja de información para el paciente propuesta al/a la niño/a
☐ Todos mis derechos han sido explicados con claridad
☐ Todos los derechos del niño han sido explicados con claridad a mí y al/a la niño/a
☐ He recibido una copia del documento de consentimiento informado
☐ He recibido una copia del documento de consentimiento informado propuesto al/a la niño/a
☐ Acepto participar en la investigación titulada "Estudio Intergrupo de BEACOPP / ABVD en la Enfermedad de Hodgkin (EORTC protocolo 20012). Estudio aleatorizado fase III del régimen BEACOPP (escalado x 4 ciclos + basal x 4 ciclos) vs. ABVD (x 8 ciclos) en pacientes con estadios III y IV con 3 o más factores de mal pronóstico según el índice pronóstico internacional " e inscrita bajo el número de estudio de la EORTC 20012. Mi participación es totalmente voluntaria y tengo la posibilidad de retirar mi consentimiento en cualquier momento sin dar explicaciones. Esto no afectará a mi relación con el médico responsable de mi tratamiento. Los datos recogidos sobre mi serán estrictamente confidenciales y se tratarán conforme a la "Directiva sobre la protección de individuos con respecto al proceso de datos personales" y las leyes aplicables locales.

Mi consentimiento no exonera a los organizadores de la investigación de sus responsabilidades y conservo todos mis derechos garantizados por la ley".

☐ Acepto que mi hijo/a participe en la investigación titulada "Estudio Intergrupo de BEACOPP / ABVD en la Enfermedad de Hodgkin (EORTC protocolo 20012). Estudio aleatorizado fase III del régimen BEACOPP (escalado x 4 ciclos + basal x 4 ciclos) vs. ABVD (x 8 ciclos) en pacientes con estadios III y IV con 3 o más factores de mal pronóstico según el índice pronóstico internacional " e inscrita bajo del número de estudio de la EORTC 20012. Su participación es totalmente voluntaria y tengo la posibilidad de retirar mi consentimiento en cualquier momento sin dar explicaciones. Esto no afectará a la relación del/de la niño/a con el médico responsable de su tratamiento. Los datos recogidos sobre él/ella serán estrictamente confidenciales y se tratarán conforme a la "Directiva sobre la protección de individuos con respecto al proceso de datos personales" y las leyes aplicables locales.

Mi consentimiento no exonera a los organizadores de la investigación de sus responsabilidades y el/la niño/a conserva todos sus derechos garantizados por la ley".

☐ He sido informado/a que los datos recogidos podrán utilizarse en el futuro para cualquier finalidad científica, asegurando la confidencialidad de los mismos.
☐ He sido informado/a que los datos recogidos sobre el/la niño/a podrán utilizarse en el futuro para cualquier finalidad científica, asegurando la confidencialidad de los mismos.
Nombre del paciente: ..............................................  
Firma del paciente: ..............................................  Fecha: ..............................................

Nombre del padre/madre/representante legal: ............................................................  
Firma del padre/madre/representante legal: ............................................................  Fecha: ..............................................

Persona designada por el investigador para participar en el proceso de consentimiento informado:

Nombre: ...............................................................  
Firma: ...............................................................  Fecha: ...............................................................  

Nombre del investigador: ...............................................................  
Cargo: ...............................................................  
Firma del investigador: ...............................................................  Fecha: ...............................................................  

El presente documento ha sido elaborado teniendo en cuenta:


Appendix K: Group Specific Appendix for the National Cancer Research Institute Lymphoma Group. (NCRI LYG)

NCRI LYG protocol number: EORTC 20012

This protocol is coordinated by the EORTC and follows the standard EORTC sequence of chapters. The chapters 1-14 of the protocol are common to all participating groups. All aspects of the protocol specific to each participating group are included under the Group Specific Appendix to the protocol. Its content should supercede chapters 15-23 (except otherwise specified).

Main contact addresses

NCRI LYG Study coordinator: Professor Barry Hancock
Dept. of Clinical Oncology, Weston Park Hospital, Whitham Road, Sheffield S10 2SJ
Phone: +44 11 42265000
Fax: +44 11 42265511
E-mail: b.w.hancock@sheffield.ac.uk

Clinical trial office: Lymphoma Trials Office
Phone: +44 20 7679 8060
Fax: +44 207679 8061
E-mail: bnli@ctc.ucl.ac.uk
1 Trial organization

This trial is an Intergroup Trial, jointly conducted by EORTC Lymphoma Group (EORTC RC) and NCRI Lymphoma Group (NCRI LYG).

♦ The EORTC RC is the coordinating group in this Intergroup trial and therefore is responsible for the trial design and activation, data management (including the quality control of data), statistical analysis and publication.

♦ NCRI LYG will use the protocol developed by EORTC. The present Group Specific Appendix details the participation of all NCRI LYG members and therefore it supercedes entirely or partially the corresponding chapters in the protocol.

♦ The NCRI LYG is collaborating group in this trial.

♦ All investigator members of the NCRI LYG will call the Lymphoma Trials Office to randomize patients.

♦ NCRI LYG will use the standard EORTC SAE definition and the standard EORTC SAE forms.

♦ The Lymphoma Trials Office will follow a “standard mail-box” procedure for this trial:

♦ Only the EORTC Data Center will code the data, perform consistency checks on data and modify them. Only the EORTC Data Center will do the analysis.

♦ There will be no direct communication between investigators members of the NCRI LYG and the EORTC Data Center.

♦ This trial is an academic trial with an educational grant from the industry.

2 Scientific matters considered as group specific and not detailed in the protocol.

♦ Patient eligibility: U.K. patients between the ages of 18-60 only, will be eligible for this trial (as approved by the EORTC).

♦ The Quality of Life assessment will not be completed in the U.K.

3 Investigator authorization procedure

All regulatory procedures must be completed in cooperation with the Lymphoma Trials Office before the investigators can be authorized to register patients in this trial.

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the Lymphoma Trials Office:

A copy of the local ethics committee approval for the study.
Each time an institution has become authorized to enter patients in this trial, the Lymphoma Trials Office will inform the EORTC Data Center. The EORTC Data Center will provide immediately the Lymphoma Trials Office with the EORTC institution number for the concerned investigator.

Patient randomization from centers not (yet) authorized will not be accepted.
4 Patient randomization procedure

Patient registration will only be accepted from authorized investigators (see "Authorization procedure").

An exhaustive list of questions to be answered during the randomization procedure is included in the Registration Checklist. The responsible investigator should complete The Registration Checklist and all the baseline forms before the patient is randomized.

All investigators should send the randomization checklist to the Lymphoma Trials Office by fax.

Lymphoma Trials Office, Fax No. +44 20 76798061

As soon as this form is received, the Lymphoma Trials Office will randomize the patients at the EORTC Data Center. The forms are first checked for any discrepancies and once resolved the patient is then randomised.

The Lymphoma Trials Office will randomize patients as described in the chapter 16 of the main protocol.

Concerning the group affiliation question:

Primary group affiliation is "NCRI LYG" for all UK investigators.

Secondary group affiliation (only applicable for institutions that include Investigators members of both, NCRI LYG and EORTC RC group participating in the trial):

♦ In case the EORTC RC is chosen as secondary group affiliation, the patients will be accounted for the EORTC RC membership (to be clearly indicated when contacting the NCRI LYG Data Center).

At the end of this procedure, the sequential identification number and the treatment will be allocated to the patient. The Lymphoma Trials Office will receive this information by an automatic E-mail and will forward it immediately to the investigators.

This sequential identification number of patient has to be recorded on all the forms. All the forms should be then sent to the Lymphoma Trials Office, which will send it to the EORTC Data Center.

5 Procedures for collecting data

The data will be reported on the EORTC forms. However, these forms will be adapted to include some NCRI LYG specific administrative information in the header.

All the Investigators participating on behalf of NCRI LYG will send all the forms to:

Ms. Lindsey Stevens
NCRI LYG Data Centre, Lymphoma Trials Office, CR UK & UCL Cancer Trials Centre, 222 Euston Road, London NW1 2DA

The Lymphoma Trials Office will follow a “mail-box” procedure for this trial.

This means that:

♦ Signed original CRFs will be collected by the Lymphoma Trials Office and sent regularly to the EORTC Data Center according to the form flow schedule (provided with the CRFs)

♦ Investigators will not be allowed to send CRFs directly to the EORTC Data Center

♦ The Lymphoma Trials Office will not modify the forms nor enter them into the computer
6 Reporting adverse events

6.1 Definitions
All NCRI LYG investigators will use the same definitions as defined in the main protocol (chapter 18.1)

6.2 Reporting procedure
All serious adverse events (SAE) related or not to the study treatment that occur during the study treatment and during the 30 days after the last study treatment administration must be reported within the 24 hours by fax to the Lymphoma Trials Office.

Any late Serious Adverse Drug Reaction (SADR), occurring after this 30 day period, should follow the same reporting procedure.

Details should be documented on the specified SAE form and need to be faxed within 24 hours to:
Address: Lymphoma Trials Office, CR UK & UCL Cancer Trials Centre, 222 Euston Road, London NW1 2DA
Fax: +44 20 7679 8061

The Lymphoma Trials Office will forward the SAE form within 24 hours to the EORTC Safety Desk (Fax: +32 2 772 8027). Any questions raised by the latter will be forwarded via the Lymphoma Trials Office. The Lymphoma Trials Office will ensure that these queries will be forwarded to the appropriate investigator and that follow-up information is also forwarded to the EORTC Safety Desk within 24 hours of receipt.

The Lymphoma Trials Office will ensure that reporting to the competent Health Authority is done according to the national regulations.

In case the Lymphoma Trials Office needs to receive Safety Reports from the EORTC Data Center, the Lymphoma Trials Office needs to distribute these Safety Reports to all participating investigators who will in turn have to inform their ERB according to the local or national law.

7 Quality assurance

7.1 Control of data consistency
NCRI LYG follows the "standard mailbox" system (see forms and procedures for collecting data). Therefore, data forms will not be entered in the database of the Lymphoma Trials Office and the Lymphoma Trials Office will not perform any consistency checks on the CRFs.

7.2 On-site quality control
A member of staff at the Lymphoma Trials Office will verify the eligibility criteria for patients entered into this trial. All forms will be checked for any omissions and returned to the centre for
correction if necessary, prior to contacting the EORTC randomisation centre. The Lymphoma Trials Office will not alter or amend the CRFs in any way.

The EORTC will perform the data timelines every 3 months. The Lymphoma Trials Office will receive the overdue tables and will contact centres on the EORTC’s behalf to request missing data or clarify any details as requested by the EORTC.

8 Ethical considerations

The trial will be run in accordance with ICH GCP guidelines. Only centres with documented local ethics approval will be allowed to randomise patients into this trial, having first obtained signed informed consent. All patients entered will be anonymised and identified by means of a unique sequential number. The patient’s name will not be asked for or recorded by the CTO.

9 Administrative responsibilities

**NCRI LYG Study coordinator:** Professor Barry Hancock, (Head of Genomic Medicine), Department of Clinical Oncology, Weston Park Hospital, Whitham Road, Sheffield S10 2SJ

Phone: +44 11 42265000  
Fax: +44 11 42265511  
E-mail: b.w.hancock@sheffield.ac.uk

**CTO:** The Lymphoma Trials Office, CR UK & UCL Cancer Trials Centre, 222 Euston Road, London NW1 2DA  
Phone: +44 20 7679 8060  
Fax: +44 20 7679 8061  
E-Mail: bnli@ctc.ucl.ac.uk

**Data Manager:** Ms Lindsey Stevens, The Lymphoma Trials Office, CR UK & UCL Cancer Trials Centre, 222 Euston Road, London NW1 2DA  
Phone: +44 20 76798062  
Fax: +44 20 76798061  
E-mail: l.stevens@ctc.ucl.ac.uk

9.1 The study coordinator

The U.K. study coordinator will be responsible for answering medical and eligibility queries from U.K. investigators.

**NCRI LYG Study coordinator:**  
Professor Barry Hancock  
*Name and address of your institution*  
Department of Clinical Oncology, Weston Park Hospital, Whitham Road, Sheffield S10 2SJ  
Phone: +44 11 42265000  
Fax: +44 11 42265511  
E-mail: b.w.hancock@sheffield.ac.uk
9.2 The Data Center

The Lymphoma Trials Office is responsible for handling investigator authorization procedure, for randomization of patients and will act as a "mail box" in this trial (see forms and procedures for collecting data). All methodological questions should be addressed to the Lymphoma Trials Office that will address them to the person competent for this trial.

The Lymphoma Trials Office is responsible for all the administrative procedures required for the trial following the normal procedures of NCRI LYG and respecting the present appendix.

The data center is also responsible, as an intermediate, to guarantee the fluent communication between the EORTC Data Center and the Investigators participating on behalf of the NCRI LYG.

Lymphoma Trials Office, CR UK & UCL Cancer Trials Centre, 222 Euston Road, London NW1 2DA

Phone No. +44 20 7679 8060
Fax No. +44 20 76798061

Statistician:

Name Dr Wendi Qian
Tel: +44 20 76704705
E-mail: wq@ctu.mrc.ac.uk

Data Manager:

Name Ms Lindsey Stevens
Tel.: +44 20 76798063
E-mail: l.stevens@ctc.ucl.ac.uk

Medical Advisor:

Name Professor Barry Hancock
Tel.: +44 11 42265000
E-mail: b.w.hancock@sheffield.ac.uk

Safety Desk:

Name Mr Paul Smith
Tel: + 44 20 76798062
Fax: + 44 20 76798061
E-mail: p.smith@ctc.ucl.ac.uk

9.3 The Group

NCRI LYG is responsible as a group to guarantee the general compliance of their members to procedures described in this appendix.

All questions concerning membership in the NCRI LYG should be addressed to the chairman and/or secretary of the NCRI LYG.

Chairman:

Professor David Linch
Address: Dept.of Haematology, 98 Chenies Mews, University College London, London WC1E 6HX
Phone: +44 20 7679 6221
Fax: +44 20 7679 6222
E-mail: d.linch@ucl.ac.uk
Secretary:
Ms. Lindsey Stevens
Address: CR UK & UCL Cancer Trials Centre, 222 Euston Road, London,
NW1 2DA
Phone: + 44 20 76798063
Fax: + 44 20 76798061
E-mail: l.stevens@ctc.ucl.ac.uk

10 Trial sponsorship and financing
*The University of Sheffield is a Legal Sponsor for all UK investigators participating in this trial.
(* Once the Department of Health has published its new, revised definition of sponsorship, it is
expected that the University of Sheffield will formally declare its intention to become a sponsor)

11 Trial Insurance for your group
There are no special compensation arrangements; however the normal National Health Service
complaints mechanism will be available to patients in this trial.

12 Patient information sheet and informed
consent
(The Multicentre Research Ethics Committee (MREC) approved versions of the patient information
sheet and consent form are included with Appendix A)

PIS version 5.0, dated 29/10/2003
Consent version 2, dated 03/02/2003
A phase III clinical trial comparing BEACOPP (4 escalated cycles+4 baseline cycles) versus ABVD (8 cycles) in advanced Hodgkin Lymphoma.

Introduction
The National Cancer Research Institute (NCRI) lymphoma study group is collaborating in a research study on patients that have a disease similar to yours. This will be an international trial supervised by doctors who are experts in the treatment of lymphoma. You are being invited to take part and this information sheet gives you details of the aims of the trial and the treatment to be given. It is important to explain why research is being done and what it will involve to help you make an informed decision whether or not to take part. Please read the following information carefully and discuss it with your doctor, family and friends if you wish. Your research nurse will also be able to give impartial advice and address any of your questions or concerns. This is an important choice for you to make. Do not feel you need to rush this decision. Please take as much time as you need. You may also want to contact the following organisations:

Consumers for Ethical Research (CERES) publish a leaflet entitled “Medical Research and You”, which gives more information about research and looks at some questions you might want to ask. A copy can be obtained from CERES, PO Box 1365, London N16 0BW. A summary of the principles of clinical trials can be found on the Cancer Research UK patient website (www.cancerhelp.org.uk). There is also an independent patient advisory group called CancerBACUP which can provide information on all aspects of cancer care (freephone 0808 8001234, 3 Bath Place, Rivington Street, London EC2A 3DR, www.cancerbacup.org).

Take time to decide whether you want to take part in this study.

What is the purpose of the study?
For many years advanced Hodgkin lymphoma has been treated with the chemotherapy drugs doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD). Chemotherapy is given to patients with this type of lymphoma both to destroy the lymphoma that is present and delay the disease returning, for as long as possible. The aim of this trial is to investigate whether a different combination of chemotherapy drugs, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone (BEACOPP) is a better treatment than ABVD. Previous studies suggest that BEACOPP may cure a greater number of patients because the treatment is more intensive than ABVD. The disadvantage of treating patients with BEACOPP is the higher risk of serious side effects. A clinical trial is therefore needed to establish whether the advantages of this new treatment outweigh the increased risk of side effects.
Why have I been chosen?

You have been diagnosed with advanced stage Hodgkin lymphoma. This is a disease that involves the lymph nodes and in your case the disease is widespread or ‘advanced’. Left untreated, Hodgkin lymphoma is a potentially life threatening disease. It should be stressed however, that in the vast majority of cases the disease can be cured with existing treatments.

How will the trial be conducted?

This is a randomised phase III trial. In order to decide whether one treatment is more effective than another we need to allocate an equal number of patients to receive each of the two treatments and compare the results. A computer programme that has no information about the individual selects the treatment to be given to each patient– i.e. by chance. This process is called randomisation. As neither you nor your doctor will be able to influence this decision we can be sure the results of the trial are not biased. Around 600 patients will be included in this trial and it has been designed to compare the effectiveness and the side effects of the two treatments. Each patient has an equal chance of receiving either ABVD or BEACOPP.

Which treatment will I get?

For this type of lymphoma we are unsure whether BEACOPP is a better treatment than ABVD. To find out which treatment is best, patients are put in to groups and their responses compared. Your doctor will let you know which treatment you have been ‘randomised’ to receive. You will not be able to choose which treatment you are given, but will have an equal chance of receiving either ABVD or BEACOPP.

What does the treatment involve?

(You may also find it helpful to refer to the diagram outlining the treatment schedule on the last page of this information sheet)

Before commencing any chemotherapy you will be assessed thoroughly by your doctor. Further tests may be required depending on the results of the physical examination. For patients randomised to receive the standard treatment, (the ABVD arm), chemotherapy drugs are given intravenously every 14 days for 8 months. In the experimental treatment in this trial (the BEACOPP arm), some drugs (bleomycin, etoposide, doxorubicin, cyclophosphamide and vincristine) are given intravenously by infusion or ‘drip’. Three intravenous infusions are given during the first week of each treatment cycle and one intravenous infusion at the beginning of the second week of each treatment cycle. Procarbazine and prednisolone are given by tablet. Each treatment cycle of BEACOPP lasts 22 days. Eight cycles will be given which will take approximately 6 months. The first 4 cycles are given at higher doses (‘escalated’ BEACOPP) than the last 4 cycles (‘baseline’ BEACOPP).

The treatment is either 8 cycles of ABVD or 4 cycles of escalated BEACOPP plus 4 cycles of baseline BEACOPP. If you agree to participate, you will be randomised to one of the treatment arms. Both ABVD and BEACOPP are usually given on an outpatient basis.

Following completion of chemotherapy you will remain under the care of a specialist in Hodgkin lymphoma. You will follow a standard pattern of outpatient visits in which you will be seen every 3 months for the first 3 years, every 6 months for the 4th and 5th years from treatment and then on an annual basis. At each visit you will have blood tests and a physical examination. CT scans of your chest, abdomen and pelvis will be done 6, 12 and 24 months after finishing treatment.

Version 5.0 Dated 29/10/2003
What are the advantages of ABVD and BEACOPP treatment?
The standard treatment for patients with your condition is ABVD. Success rates are good and many patients are cured with this treatment. Fertility is effected by ABVD but to a lesser degree than treatment with BEACOPP. ABVD has been used for many years so the side effects are well known and can be anticipated. There is less risk of serious side effects with ABVD than BEACOPP. Treatment with BEACOPP has two important advantages over the standard treatment. The first is that it may cure a greater number of patients than ABVD and delay the disease returning. It may also decrease the risk of long term side effects to the heart and lung that effect a small number of patients.

What are the disadvantages and possible risks of ABVD and BEACOPP treatment?
Patients treated with ABVD and BEACOPP are at risk of high toxicity, side effects and other hazards. Both treatments effect male and female fertility. This is a major concern for female patients because there is little chance of fertilising an egg that has been frozen. The risk of infertility in women is slightly higher with BEACOPP treatment than ABVD. Male patients will be given the opportunity to have their sperm frozen and stored in a sperm bank before treatment with ABVD or BEACOPP begins. Again there is a higher risk of infertility in men with BEACOPP compared to ABVD. Both ABVD and BEACOPP could damage an unborn child. For this reason male and female patients of childbearing age must take adequate contraceptive measures for the duration of therapy.

Chemotherapy also reduces the number of white cells in the blood. These cells fight infection and are an important part of the body’s natural immune system. A reduction in their number means that patients are more prone to infection. This reduction of white blood cells is called ‘neutropenia’. BEACOPP treatment is more intensive than ABVD so its side effects, including neutropenia, are more severe. Neutropenia lasts longer in patients treated with BEACOPP than those treated with ABVD. This means there is a greater risk of infection, which may be dangerous and even life threatening. In order to prevent this, a substance called G-CSF is given once a day by injection. Patients experience bony aches and discomfort at the site where the injection is given but these side effects stop on completion of the injections.

Regardless of which treatment is given all patients will receive two additional CT scans by taking part in this study. This means patients will be exposed to more radiation than if they were not being treated as part of a clinical trial. The radiation risk is considered to be small although the risk is slightly higher for younger patients. In the longer term, there is some evidence that a small proportion of patients treated with ABVD may develop heart or lung problems late in life. This risk is reduced with BEACOPP treatment. Both treatments cause reversible hair loss and nausea.

What are the possible benefits of taking part?
We hope that both treatments will treat your lymphoma effectively but there is no guarantee of this. Your cancer may shrink, the chance of your cancer returning may be reduced and you may live longer with a better quality of life. This is impossible to predict. The information we get from this study may help us treat patients with this type of lymphoma better in the future.

Do I have to take part?
Your participation in this trial is entirely voluntary. 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 to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw from the trial, or a decision not to take part, will not affect the standard of care you receive.
**Will my taking part in this study be kept confidential?**

This trial will be run in accordance with current data protection legislation. Any information about you that is collected during the study will be kept strictly confidential. Data relating to the trial taken from the hospital will have your name removed so that you cannot be recognised from it. We will also ask your permission to pass details of your treatment to your GP. In order to confirm the initial diagnosis of your disease a central pathology review is required. This means that some of the tissue taken to make the diagnosis of your disease will be sent from your hospital. The pathologist who receives this will not be able to identify you from this sample. These samples will be stored at the Haematological Malignancy Diagnostic Service in Leeds. You retain rights to these samples and no future research will be done using this tissue unless your consent is obtained.

**What if new information becomes available?**

Sometimes, during the course of a research project new information becomes available about the treatment that is being studied. If new information about treatment for your type of lymphoma becomes available during the course of this trial your doctor will tell you about it and discuss whether you want to continue in the study. If you decide to withdraw from the study your research doctor will make arrangements for your care to continue. If new side effects of the treatment come to light, or your doctor feels the treatment is no longer in your best interest, treatment will be stopped and an alternative treatment offered. Your participation in this trial is entirely voluntary. A decision to withdraw at any time will not affect the standard of care you receive.

**What happens when the research stops?**

If the trial is stopped for any reason your doctor will discuss your treatment with you. Alternative treatment with combination chemotherapy would probably be offered.

**What happens if something goes wrong?**

If you are harmed by taking part in this research project there are no special compensation arrangements. If you are harmed by someone’s negligence, then you may have grounds for legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the care you have received during this study, the normal National Health Service complaints mechanism may be available to you.

**What happens to the results of the study?**

We hope the study will be completed in 5 years. The results of the study will be published in a major medical journal about 3 years after the study has closed. When the results are published it will not be possible to identify any of the patients who took part.

**Who is organising and funding the research?**

The National Cancer Research Institute lymphoma study group is organising this trial. It is managed by the Cancer Research U.K. and University College London lymphoma trial office. There is no pharmaceutical industry funding.
**Who has reviewed the research?**

Independent experts, as part of the European Organisation for the Research and treatment of Cancer protocol review process, have reviewed this trial to ensure that it is scientifically valid. All research involving human subjects has to be reviewed by an Ethics Committee before it can take place. This study has been reviewed by the Thames Valley Medical Research Ethics Committee and by your hospital’s own Ethics Committee.

**Who should I contact if I require Further Information?**

Please contact…………………..(Telephone Number…………………..)

Thank you for reading this information sheet. You will be given a copy to take with you should you decide to participate in the trial.
ABVD treatment takes approximately 8 months to complete.

BEACOPP treatment takes approximately 6 months to complete.

**TREATMENT CYCLE 1–8**
- Adriamycin 25mg/m² intravenous infusion, (i.v) Day 1 & 15
- Bleomycin 10mg/m² (i.v) or intramuscular (i.m) Day 1 & 15
- Vinblastine 6mg/m² (i.v) Day 1 & 15
- Cyclophosphamide 375mg/m² (i.v) Day 1 & 15
  - (G-CSF injection given if required)

(The duration of each cycle is 28 days)

**TREATMENT CYCLE 1–4 (Escalated dose)**
- Bleomycin 10mg/m² (i.v, i.m) Day 8
- Etoposide 200mg/m² intravenous infusion (i.v) Day 1–3
- Adriamycin 35mg/m² (i.v) Day 1
- Cyclophosphamide 1250mg/m² (i.v) Day 1
- Oncovin (vincristine) 1.4 mg/m² (i.v) Day 8
- Procarbazine 100mg/m² (tablet, by mouth) Day 1–7
- Prednisolone 40mg/m² (tablet, by mouth) Day 1–14

(The duration of each cycle is 22 days)

**TREATMENT CYCLE 5–8 (Baseline dose)**
- Bleomycin 10mg/m² (i.v, i.m) Day 8
- Etoposide 100mg/m² intravenous infusion (i.v) Day 1–3
- Adriamycin 25mg/m² (i.v) Day 1
- Cyclophosphamide 650mg/m² (i.v) Day 1
- Oncovin (vincristine) 1.4 mg/m² (i.v) Day 8
- Procarbazine 100mg/m² (tablet, by mouth) Day 1–7
- Prednisolone 40mg/m² (tablet, by mouth) Day 1–14

(The duration of each cycle is 22 days)
PATIENT CONSENT FORM

A phase III clinical trial comparing BEACOPP (4 escalated cycles + 4 baseline cycles) versus ABVD (8 cycles) in advanced Hodgkin Lymphoma.

☐ I confirm that I have read and understood the information sheet (version 3.0 dated 03.02.2003) for the above study and that I have been given the opportunity to ask questions.

☐ I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving a reason, without my medical care being affected.

☐ I understand that my doctor will make details of my treatment available to members of the trial management team. These details will be collected on a Case Report Form and the only form of identification on these forms will be a Unique Patient Number (UPN) and my date of birth. I give my permission for these individuals to have access to this information.

☐ I agree that anonymised biopsy material may be sent for central pathology review to confirm the initial diagnosis. I understand that I retain rights to these samples and can request in the future that these samples are returned to my hospital or destroyed.

☐ I consent to details of my treatment being made available to my GP.

☐ I agree to take part in the above study.

________________________ ____________________ ________________
Name of patient   Signature   Date

________________________ ____________________ ________________
Name of person taking consent   Signature   Date
(If different from researcher)

________________________ ____________________ ________________
Name of researcher   Signature   Date

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

Version 2.0 Dated 03/02/200
Appendix L: ALLG Group Specific Appendix
EORTC protocol 20012

Australasian Leukaemia
and Lymphoma Group
protocol number HD04

This protocol is coordinated by the EORTC and follows the standard EORTC sequence of chapters. The chapters 1-14 of the protocol are common to all participating groups. All aspects of the protocol specific to each participating group are included under the Group Specific Appendix to the protocol. Its content should supersede chapters 15-22 (except otherwise specified).

ALLG Study coordinators:  
Dr Max Wolf  
Division of Haematology and Medical Oncology, Peter MacCallum Cancer Centre,  
St Andrews Place, East Melbourne, Victoria 3002 Australia  
Phone: +613 9656 1087  
Fax: +613 9656 1408  
E-mail: Max.Wolf@petermac.org

ALLG Trial Centre:  
Janey Stone  
ALLG Trial Centre, Peter MacCallum Cancer Centre, St Andrew’s Place, East Melbourne, Vic 3002 Australia  
Phone: +613 9656 1265  
Fax: +613 9656 1420  
e-mail: Janey.Stone@petermac.org
1 Trial organization

This trial is an Intergroup Trial, jointly conducted by EORTC and ALLG.

- The EORTC is the coordinating group in this Intergroup trial and therefore is responsible for the trial design and activation, data management (including the quality control of data), statistical analysis and publication.

- ALLG will use the protocol developed by EORTC. The present ALLG Group Specific Appendix details the participation of all ALLG members and therefore it supersedes entirely or partially the corresponding chapters in the protocol.

- The ALLG is a collaborating group in this trial.

- ALLG is the legal sponsor for all their members. Only ALLG can authorize these investigators to randomize patients.

- All investigators of the ALLG will call the ALLG Trial Centre to randomize patients.

- ALLG will use the standard EORTC SAE definition and the standard EORTC SAE forms.

- Only the EORTC Data Center will code the data, perform consistency checks on data and modify them. Only the EORTC Data Center will do the analysis.

2 Scientific matters considered as group specific and not detailed in the protocol.

- In accordance with ALLG policy, all participating centres are encouraged to submit the generic ALLG Tissue Bank consent form to their ethics committees, and then offer all patients participating in this study the opportunity to also provide tissue to the ALLG Tissue Bank.

- All patients participating in this study in Australia will receive pegfilgrastim mandated for the 4 cycles of escalated BEACOPP and optional for baseline BEACOPP and ABVD. All patients with anaemia will also receive darbepoetin alfa. This group specific component will be conducted in conjunction with Amgen Australia.

**Pegfilgrastim**

Escalated BEACOPP: Pegfilgrastim 6 mg SC on day 9 (the day after bleomycin administration).

Baseline BEACOPP and ABVD: Patients who experience an episode of febrile neutropenia or prolonged severe neutropenia (neutrophil count of less than 1.0 x 10^9 cells/L), and for whom there is clinical justification for continuing the planned chemotherapy, will receive pegfilgrastim 6 mg SC on the day after completion of chemotherapy in all subsequent cycles (day 9 for baseline BEACOPP and day 2 for ABVD).

**Darbepoetin alfa**

Patients with a haemoglobin less than 110 g/L will receive darbepoetin alfa given once per cycle as a single SC injection. Darbepoetin alfa can be given on day 1 of chemotherapy, prior to administration of chemotherapy. The aim of treatment is to increase haemoglobin concentration and to reduce the requirement for transfusions.

The dose of darbepoetin alfa will be a single dose of 300 µg every two weeks during ABVD chemotherapy, and a single dose of 500 µg every three weeks during escalated or baseline BEACOPP.
Dosage Adjustments:

The dose should be adjusted to achieve and maintain a target haemoglobin in the range 110-120 g/L. If the increase in haemoglobin is inadequate (less than 10 g/L after approximately 6 weeks of therapy, unless the haemoglobin is in the target range) or if the response is not satisfactory in terms of reducing red blood cell transfusion requirements, the dose of darbepoetin alfa should be increased. Patients being treated with ABVD already receiving a single dose of 300 µg will be given a single dose of 500 µg every two weeks; patients being treated with either escalated or baseline BEACOPP already receiving a single dose of 500 µg every three weeks will have the frequency of administration increased to 500 µg every two weeks. If haemoglobin increases by more than 10 g/L in a 2-week period the dose should be reduced by approximately 25%. If haemoglobin exceeds 130 g/L, doses should be temporarily withheld until the haemoglobin falls to 120 g/L. At this point, therapy should be re-instated at a dose approximately 25% below the previous dose.

3 Investigator authorization procedure

All regulatory procedures must be completed in cooperation with the ALLG Trial Centre before the investigators can be authorized to register patients in this trial.

Investigators will be authorized to register or randomize patients in this trial only when they have returned to the ALLG Trial Centre:

- Commitment Statement
- Financial Statement
- Signature Log
- Ethics approval letter
- Normal laboratory values

Each time an institution has become authorized to enter patients in this trial, the ALLG Trial Centre will inform the EORTC Data Center and provide the EORTC Data Manager with

- the Signature Log
- the normal laboratory values of the centre.

The EORTC Data Center will provide immediately the ALLG Trial Centre with the EORTC institution number for the concerned investigator.

Patient registration/randomization from centers not (yet) authorized will not be accepted.

4 Patient randomization procedure

Patient registration will only be accepted from authorized investigators (see "Authorization procedure").

An exhaustive list of questions to be answered during the randomization procedure is included in the Registration Checklist. The responsible investigator should complete the Registration Checklist and all the baseline forms before the patient is randomized.
All investigators members of ALLG should send the randomization checklist to the ALLG Trial Centre by fax.

Janey Stone
Fax: 03-9656 1420 (international: +613 9656 1420)

As soon as this form is received, the ALLG Trial Centre will randomize the patients at the EORTC Data Center.

The ALLG Trial Centre will randomize patients as described in the chapter 16 of the main protocol.

Concerning the group affiliation question: primary group affiliation is " ALLG "

At the end of this procedure, the sequential identification number and the treatment will be allocated to the patient. The ALLG Trial Centre will receive this information by an automatic E-mail and will transcribe this information on the Randomization Checklist. The ALLG Trial Centre will immediately forward this completed Checklist to the investigators and to the EORTC Data Center.

The allocated sequential identification number of patient has to be recorded on all the forms. All the forms should be then sent directly to the EORTC Data Center.

5 Procedures for collecting data

The data will be reported on the EORTC forms. However, these forms will be adapted to include some ALLG specific administrative information in the header.

All the Investigators participating on behalf of ALLG will send all the forms to:

Hodgkin's Lymphoma Data Manager
EORTC Data Center
avenue Emmanuel Mounier, 83, bte 11
B-1200 Brussels, Belgium

Signed original CRFs will be sent regularly to the EORTC Data Center according to the form flow schedule (provided with the CRFs)

The EORTC Data Center will enter the data in the computer for quality control and analysis. When necessary, queries will be transmitted to the ALLG investigators, who will send their answer back to the EORTC Data Center.
6 Reporting adverse events

6.1 Definitions
All ALLG investigators will use the same definitions as defined in the main protocol (chapter 18.1)

6.2 Reporting procedure
All serious adverse events (SAE) related or not to the study treatment that occur during the study treatment and during the 30 days after the last study treatment administration must be reported within the 24 hours by fax to the EORTC Safety Desk (Fax: +32 2 772 8027).

Any late Serious Adverse Drug Reaction (SADR), occurring after this 30 day period, should follow the same reporting procedure.

Details should be documented on the specified SAE form. Any questions raised will be sent to the appropriate investigator directly who will send follow-up information to the EORTC Safety Desk within 24 of receipt.

All SAEs should also be faxed within 24 hours to:

NAME: Janey Stone
ALLG Trial Centre
Fax: 03-9656 1420 (international +613 9656 1420)

The ALLG Trial Centre will ensure that reporting to the competent Health Authority is done according to the regulations of the appropriate country/ies.

Reporting Procedures for Serious Adverse Events Related to Pegfilgrastim (Neulasta®) or Darbepoetin alfa

All serious adverse events judged related to pegfilgrastim or darbepoetin alfa must be sent or faxed to the TGA (address listed below) within 15 calendar days of discovery or notification of the event using the ADRAC ‘blue card’ which can be downloaded from:

The Secretary, ADRAC
Reply Paid 100
Woden ACT 2606
Fax: (02) 6232 8392

A copy of the report must also be faxed or sent to Clinical Safety, Amgen Australia within 1 working day to:
Clinical Safety Department
Amgen Australia Pty Ltd
Level 1, 801 Glenferrie Road
Hawthorn VIC 3122
Fax: (03) 9818 5123
Ph: (03) 9854 9800
All serious and medically significant adverse events considered related to pegfilgrastim or darbepoetin alfa by the investigator will be followed until resolved or considered stable. The following attributes must be assigned: description; dates of onset and resolution; severity; assessment of relatedness to pegfilgrastim or darbepoetin alfa and action taken.

The investigator should notify the Institutional Ethics Committee of serious adverse events occurring at the site, in accordance with local procedures.

It will be left to the investigator's clinical judgment whether or not an adverse event is of sufficient severity to require that the subject should be removed from treatment. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable adverse event. If either of these occur, the subject must undergo an end-of-study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

Any pregnancy occurring during this study should be immediately reported to Clinical Safety, Amgen Australia.

The ALLG Trial Centre will receive Safety Reports from the EORTC Data Center, and distribute these to all participating investigators who will in turn have to inform their ERB according to the local or national law.

7 Quality assurance

7.1 Control of data consistency

Data forms will not be entered in the database of the ALLG Trial Centre and the ALLG Trial Centre will not perform any consistency checks on the CRFs.

7.2 On-site quality control

No on-site quality control is foreseen for this trial.

7.3 External review of histology

According to the protocol (19:2), the participating centre must send either fifteen (15) unstained sections or paraffin blocks together with the original pathology form to the ALLG Trial Centre. The ALLG Trial Centre will forward the material to the Panel Committee address (see main protocol).

7.4 Other quality controls

The EORTC will perform the data timelines every 3 month. ALLG Trial Centre will receive the overdue tables and notify the relevant investigator/data manager at affected centres.

8 Ethical considerations

♦ The principal investigator at each participating institution is responsible for ensuring that this study is conducted in agreement with the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments).

♦ The protocol has been written and the study will be conducted according to the ICH Harmonised Tripartite Guideline for Good Clinical Practice (ref: http://www.ifpma.org/pdf/ifpma/e6.pdf)

♦ Each institution must have approval for the study from the local Human Research Ethics Committee.
The study will be conducted in accordance with all relevant privacy legislation. The name of the patient will not be asked for nor recorded at the ALLG Trial Centre. It will be the responsibility of each institution to maintain a register of all patients entered into the trial. This register must be kept in a secure and identifiable location. Approximately once a year, the ALLG Trial Centre will request confirmation that the register is being maintained accurately and is up to date. A sequential identification number will be automatically assigned to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, the patient's initials, date of birth and local medical record number will also be reported on the case record form.

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician. A draft of a suitable patient information and consent form is included with this ALLG Group Specific Appendix.

It will be emphasized that participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient’s subsequent care. Documented informed consent will be obtained for all patients included in the study before they are registered or randomized at the EORTC Data Center. This will be done in accordance with Australian or New Zealand national and local regulatory requirements as appropriate.

### 9 Administrative responsibilities

#### 9.1 ALLG Principal Investigator

The Study Coordinator of ALLG will be responsible for making all decisions relating to questions of interpretation of the protocol including eligibility, treatment and the evaluation of patients.

**ALLG Principal Investigator:**

Dr Max Wolf  
Division of Haematology and Medical Oncology  
Peter MacCallum Cancer Centre  
St Andrew’s Place, East Melbourne, Vic 3002, Australia  
Phone: +613 9656 1087  
Fax: +613 9656 1408  
E-mail: Max.Wolf@petermac.org

#### 9.2 The Trial Centre

The ALLG Trial Centre is responsible for handling investigator authorization procedure, overseeing trial approval by institutional Human Research Ethics Committees, and for randomization of patients. All methodological questions should be addressed to the ALLG Trial Centre that will address them to the person competent for this trial. All protocol related queries should also in the first instance be directed to the Trial Centre.

The ALLG Trial Centre is responsible for all the administrative procedures required for the trial following the normal procedures of ALLG and respecting the present appendix.
The Trial Centre is also responsible, as an intermediary, to guarantee the fluent communication between the EORTC Data Center and the Investigators participating on behalf of the ALLG.

The Trial Centre will provide all participating centres in Australia with detailed procedural information and will coordinate the supply of pegfilgrastim and darbepoetin alfa in association with Amgen Australia.

**ALLG TRIAL CENTRE**

Centre for Biostatistics and Clinical Trials  
Peter MacCallum Cancer Centre  
St Andrews Place, East Melbourne, Victoria 3002, Australia  
Tel: + 613 9656 1265  
Fax: + 613 9656 1420

**Statistician:**  
Name: Dr John Reynolds  
Tel: +613 9656 1649  
E-mail: John.Reynolds@petermac.org

**Data Manager:**  
Name: Ms Janey Stone  
Tel.: +613 9656 1265  
Fax: +613 9656 1420  
E-mail: Janey.Stone@petermac.org

**Medical Advisor:** No Medical Advisor  
**Safety Desk:** No Safety Desk

### 9.3 The Group

ALLG is responsible as a group to guarantee the general compliance of their members to procedures described in this appendix. The group will ensure that all participating institutions are notified of their responsibilities in relation to this trial, and that they will provide a written commitment that they will comply.

All questions concerning membership in the ALLG should be addressed to the chairman and/or secretary of the ALLG.

**Chairman:**  
Dr Max Wolf  
Division of Haematology and Medical Oncology  
Peter MacCallum Cancer Centre  
St Andrew’s Place, East Melbourne, Victoria 3002, Australia  
Phone: +613 9656 1087  
Fax: +613 9656 1408  
E-mail: Max.Wolf@petermac.org
9.4 Pharmaceutical company support

Amgen Australia will donate the Neulasta® (pegfilgrastim) required for the 4 cycles of escalated BEACOPP and for those patients for whom Neulasta® is not available under reimbursement for the baseline BEACOPP and ABVD. Amgen Australia will also donate the darbepoetin alfa for patients with anaemia. Procedures for ordering the drugs will be provided to all participating centres.

For all information relating to Neulasta® or darbepoetin alfa, contact:

Dr Robert Mrongovius
Amgen Australia
Level 1, 801 Glenferrie Road, Hawthorn, Victoria 3122, Australia
Phone: +613 9854 9818
Fax: +613 9818 5123
E-mail: robert@amgen.com

10 Trial sponsorship and financing

♦ ALLG is the Legal Sponsor for all investigators participating on behalf of the ALLG. As such, the ALLG shall be responsible for compliance with clinical and/or regulatory procedures in the ALLG Trial Centre and will obtain copies of all relevant regulatory documents from the Study Centres. The ALLG will inform the Study Centers of their obligations in relation to clinical and/or regulatory procedures and will obtain from each Study Centre a signed agreement to comply with these procedures.

♦ Amgen Australia has provided financial support for this study, which includes a grant for each institution of $300 Australian per patient entered. The payments will be coordinated by the ALLG Trial Centre and detailed information on procedures will be provided to all participating centres.

11 Trial Insurance for ALLG

The ALLG will ensure that all participating centres have appropriate insurance for patients entered into this study. Any centre which is unable to provide appropriate coverage will not be permitted to participate.

12 Patient information sheet and informed consent
PARTICIPANT INFORMATION SHEET
and consent form

Site:

Full Project Title: Title of the research protocol: Intergroup Hodgkin BEACOPP / ABVD study (EORTC protocol 20012). A phase III randomized study of BEACOPP (escalated x 4 cycles + baseline x 4 cycles) versus ABVD (x 8 cycles) in Unfavorable stage III & IV patients stratified on the International Prognostic Score as IPS 3 or more.

Please make sure you have all .... pages of this document.

1. Your Consent

This Participant Information Sheet contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Participant Information Sheet carefully. Feel free to ask questions about any information in the Information Sheet. Before deciding whether or not to take part, you may wish to discuss the project with a relative or friend or your local health worker.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of both the Consent Form and this Participant Information Sheet to keep as a record.

2. Purpose and Background

You are being invited to participate in this research study because you have a disease called Hodgkin lymphoma (Hodgkin’s disease). The tests which you have already had showed that the disease is involving lymph nodes in both the upper and lower parts of your body or even organs which are not of lymphoid origin such as bone marrow, lungs or liver. In many patients this disease can be cured with chemotherapy.

The current standard chemotherapy regimen is called “ABVD” which has been used for the treatment of this disease for over 20 years in Australia and elsewhere. It consists of four drugs doxorubicin, bleomycin, vinblastine and dacarbazine, which are given every 2 weeks by intravenous (into a vein) infusion for a total of up to 8 months. The aim of the treatment is to obtain a complete remission which means that all the disease has gone from your body, and to prevent the disease from coming back once the treatment stops.

Studies performed in Germany have indicated that a more intense chemotherapy regimen called BEACOPP may produce even better results than ABVD. This consists of these seven drugs: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone. These are given every 3 weeks for 8 courses over 6 months. However, the two regimens ABVD and BEACOPP have never been directly compared to each other.

The aim of this study is to compare the standard ABVD treatment with the BEACOPP treatment to see which of the two treatments is better and which produces less side effects. The first 4 cycles of
BEACOPP are given at higher doses (“escalated” BEACOPP) than the last 4 (BEACOPP “baseline”). Doctors all over Europe, Canada, Australia and New Zealand will treat their patients according to this clinical research project. Over a period of 5 years a total of 600 patients will be treated on this research study. In Australia and New Zealand, this study is being conducted by the Australasian Leukaemia and Lymphoma Group (ALLG).

No individual researcher will gain direct financial benefit from conducting this study.

3. Procedures

Pre Treatment

Before treatment starts you will undergo a series of tests in order to determine whether you are eligible to participate in this study. None of these tests are experimental and are standard tests for your disease. Once you are deemed eligible by your study doctor you will be registered to the study and you will be able to receive the treatment.

The tests include:

♦ Physical examination

♦ Blood samples (approximately 2½ tablespoons of blood): for routine tests such as blood cell counts, to check organ function and for tests for various past viral infections.

♦ CT scan (computerized tomography) and/or ultrasound of your head and neck, chest, abdomen and pelvis.

♦ Bone marrow biopsy - consists of an injection of local anaesthetic that makes the skin and bone marrow surface numb. A needle is then placed into the back of the hip, and a sample of blood from inside the bone (containing blood producing cells) and a small core of bone are taken. You may be given a sedative before the procedure. The procedure takes about 15 minutes and no stitches are required. The procedure can be uncomfortable and can result in bleeding or bruising.

♦ Heart scan known as a Left Ventricular Ejection Fraction (LVEF) – to evaluate how well your heart chambers fill with blood and pump it to the rest of the body. A LVEF scan involves injection of a small amount of radioactive chemical and use of a special scanner to determine the flow of the chemical through the heart. You will need to lie down on a table under the scanner for approximately 20 minutes.

♦ Electrocardiograph (ECG) – a recording of the electrical activity of your heart.

♦ Lung function will be evaluated.

♦ To verify the initial diagnosis (done by the pathologist in your hospital), glass slides of tumour biopsy (taken at the time of establishing the diagnosis) will be sent to an expert pathologist who is situated in Europe. In some cases, when it is difficult to confirm the diagnosis, a frozen sample of your tumour biopsy will be sent to the expert pathologist. This material will be used to prepare new slides and perform additional diagnostic investigation. All your samples will only be identified by a patient number assigned to you and the first two letters of your first name and the first three letters of your surname.
**Description of Treatment**

If you agree to participate in this study, you will be randomised to be treated with either the ABVD or the BEACOPP regimen. Randomisation means that you are put into a group by chance. It is like flipping a coin. Neither you nor your doctor can decide which treatment you will receive. You have an equal chance of being placed in either group.

In the ABVD arm, the chemotherapy medications are administered intravenously twice a month (one cycle) for a total of 8 months.

In the BEACOPP arm, some drugs (bleomycin, etoposide, doxorubicin, cyclophosphamide and vincristine) are given intravenously (three intra venous injections during first week and one intra venous injection at the beginning of second week for each three-weekly cycle). Procarbazine and prednisone are given orally (by mouth). New cycles are given every 21 days.

Before each chemotherapy cycle there will be a physical check-up with a blood count check together with lung & heart function. A chest x-ray will be done if clinically indicated.

After cycle 4 and cycle 6, the following examinations need to be done: blood check (counts and biochemistry), physical examination, radiological (CT scan) examination of your chest, abdomen & pelvis. If your bone marrow and/or liver had Hodgkin’s disease before starting the treatment, they will need to be examined again.

At the end of treatment (full treatment is 8 cycles) the same test will need to be performed so that your response to treatment can be fully documented.

After finishing the protocol treatment, you will need to come for a check every three months in the first three years. In the years 4 and 5 check up will be every 6 months and after five years, annual visits will be performed. During the visits the following will be checked: blood check (counts and biochemistry), physical examination, CT scan examination of your chest, abdomen & pelvis (this well be done 6, 12 and 24 months after finishing treatment).

By consenting to participate in this study, you consent to the various blood tests, other tests and analyses for the purposes noted above.

4. **Possible Outcomes/Potential Benefits**

We cannot guarantee or promise that you will receive any benefits from taking part in this study, but other patients may benefit in the future from information gained from it.

If your disease becomes worse, if side effects become severe, if new information indicates that this treatment is not in your best interest, or your doctor feels that this treatment is no longer in your best interest, the treatment will be stopped. Further treatment will be discussed. If new side effects or information about your disease or treatment are discovered during the study, you will be told.
5. Possible Risks

If you participate in this clinical research study, your doctor will observe you carefully for the development of any side effects. Any side effects you develop will be assessed thoroughly and treated appropriately by your doctor. Any unusual symptoms or side effects that you experience should be reported to your doctor.

The main side effects of the ABVD chemotherapy are: a reversible hair loss and the lowering of the blood cell counts (white cells, red cells, platelets). A low white cell count makes patients vulnerable to infections. If you have a fever (over 38C) you should notify your doctor or research nurse.

Low red blood cell count is called anaemia, and low platelets can cause a bleeding tendency. Occasionally patients require a transfusion with red cells or platelets if the red cell count or platelet count is significantly reduced. Nausea and vomiting are also very common, however they are generally controlled with anti-sickness treatment that you will be given.

Lung problems such as cough and shortness of breath can occur due to the drug bleomycin and your lung function will be closely monitored.

Heart problems (shortness of breath, tiredness, cough, swollen ankles) can occur months or years after you finish the chemotherapy due to the drug doxorubicin. The total dose of doxorubicin which you will receive will be below the dose which usually causes heart problems and you will be monitored for development of heart problems.

The BEACOPP treatment arm is more intensive and therefore the side effects of the treatment can be more severe than with ABVD. You may be given a blood hormone G-CSF to try and prevent low white blood counts. There is a also a higher risk of infertility in men and of sterility and early menopause in women aged over 30 years. In very rare instances, late effects may result in permanent bone marrow damage or even cause leukaemia some years later.

The effects of chemotherapy on the unborn child and on the newborn baby are not known. Because of this, it is important that study participants are not pregnant or breast-feeding and do not become pregnant during the course of the study. If you are male, you should not father a child. If you are female and child bearing is a possibility, you may be required to undergo a pregnancy test prior to commencing the study. Both male and female participants are strongly advised to use effective contraception during the course of the study and for a period of 3 months after completion of the study. You should discuss methods of effective contraception with your doctor. If you do become pregnant whilst participating in the study you should advise your treating doctor immediately. He/she will withdraw you from the study and advise on further medical attention should this be necessary. Chemotherapy may cause temporary or permanent sterility. Please discuss this with your doctor if you have any concerns about future fertility.

The side effects of chemotherapy will be closely monitored and the dose of drugs adjusted according to degree of symptoms. In some cases a drug will be removed from the regimen and possibly replaced by another. In very severe cases the protocol treatment will stop. In such a case further treatment options will be discussed with you.
The side effects of chemotherapy will be closely monitored and the dose of drugs adjusted according to degree of symptoms. In some cases a drug will be removed from the regimen and possibly replaced by another. In very severe cases the protocol treatment will stop. Further treatment will be upon the investigators discretion and in the best interest of the patient.

There may be other side effects that are not foreseen at this time.

6. Alternatives to Participation

Treatment options other than participation in this trial are available to you. Both ABVD and BEACOPP are standard treatments and one of these would be offered to you if you do not wish to participate. Generally, ABVD is more widely used in Australia for patients not on study. Your doctor will discuss the available alternatives with you prior to you making a decision.

7. Other Treatment Whilst on Study

It is important that you tell your doctor about any treatments or medications you may be taking including non-prescription medications, vitamins or herbal remedies, acupuncture or other alternative procedures and any changes to these during your participation in the study.

8. Privacy, Confidentiality and Disclosure of Information

As part of this trial it may be necessary for some of your health information to be obtained from other health service providers, for example from another hospital, a private pathology laboratory, a radiographer or radiotherapist, your GP or a consultant. This may include the provision of a copy of your CT scan. By consenting to participate in this study you agree to your general practitioner and other entities referred to above being contacted and/or disclosing further health information about you and the obtaining of a copy of your CT scan.

Access:

The trial involves the collection of information contained in your medical records and which relate to your disease. It is very important that the information collected is accurate and from time to time it may be checked against your medical records. Duly authorized persons (EORTC staff, national and/or foreign health authority representatives or certain persons from the company supplying the trial medication) may have access to your medical records. All information will be strictly confidential and your identity will never be divulged, you have the right to access this information according to the laws applicable in Australia.

It is desirable that your family doctor be advised of your decision to participate in this research project. By signing the Consent Form, you agree to your family doctor being notified of your decision to participate in this research project.
9. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

10. Results of Project

It is usual for a number of years to elapse before definitive results of this type of study are available. These are published in medical journals that are available to the public. You should feel free to ask your doctor about this. A plain English summary of the study results will be made available to you if you wish.

11. Further Information or Any Problems

The doctor you should contact should any medical problems arise is Dr ……………... The hospital telephone number is ……………... During working hours, you can also call the hospital and ask for Research Nurse ……………... on pager…………...If after hours, ask for the haematologist on call.

If you seek emergency care, or if you are hospitalised, please alert the doctor who is treating you that you are enrolled in a research study being conducted by ……………... at the ……………....

12. Other Issues

Ethical concerns can be discussed with…………………………………………………………………

13. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with……………………………………...

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Sign the Consent Form only after you have had a chance to ask your questions and have received satisfactory answers.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.
14. Reimbursement of your costs
You will not be paid for your participation in this trial. You will only be required to pay for the prescription fee associated with the dispensing of any drug that you would normally have as part of standard treatment for your disease, outside of the study.

15. Injury
In the event that you suffer an injury as a result of participating in this trial, hospital care and treatment will be provided by the public health service at no extra cost to you.

16. Termination of the study
This clinical trial may be ended for a variety of reasons. These may include such reasons as unacceptable side effects, one arm of the study being shown to be better and decisions made in the commercial interests of the sponsor.

17. Ethical Guidelines
This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

All aspects of this research project have been approved by Ethics Committee of the 

.................................
Consent Form
Version 1 Dated .................

Full Project Title: Intergroup Hodgkin BEACOPP / ABVD study (EORTC protocol 20012). A phase III randomized study of BEACOPP (escalated x 4 cycles + baseline x 4 cycles) versus ABVD (x 8 cycles) in Unfavorable stage III & IV patients stratified on the International Prognostic Score as IPS 3 or more.

Principal Researcher: ........................................

I have read, or have had read to me in my first language, and I understand the Participant Information Sheet version 1 dated .................

I have had an opportunity to ask questions about this research project and am satisfied with the answers I have received.

I freely agree to participate in this project according to the conditions in the Participant Information Sheet.

I have a copy of the Participant Information Sheet and the Consent Form to keep.

I understand the researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

I agree not to participate in other clinical studies during my participation in this trial.

I understand that it may be necessary for some of my health information to be obtained from other health service providers, for example from another hospital, a private pathology laboratory, a radiographer or radiotherapist, my GP or a consultant.

I understand that by signing this consent form I authorize the release of/or access to this confidential information to the relevant study personnel and regulatory authorities as stated in the conditions.

Participant’s Name (printed) ........................................................................................................................................

Signature .......................................................... Dated .....................................................

Name of Witness to signature (printed) ......................................................................................................................................

Signature .......................................................... Dated .....................................................

Researcher’s Name (printed) ........................................................................................................................................

Signature .......................................................... Dated .....................................................

Version 1
19 February 2004
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