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Analysis of Data Collected in the European Group for Blood and Marrow Transplantation (EBMT) Registry on a Cohort of Patients Receiving Plerixafor

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ABBREVIATIONS

ARDS	acute respiratory distress syndrome
BM	bone marrow
CPMP	Committee for Proprietary Medicinal Products
CR	complete remission
EBMT	European Group for Blood and Marrow Transplantation
EBV	Epstein-Barr virus
EMA	European Medicines Agency
EU	European Union
FLIPI	Follicular Lymphoma International Prognostic Index
G-CSF	granulocyte colony stimulating factor
GF	growth factor
GvHD	graft versus host disease
HSC	haematopoietic stem cell
HSCT	haematopoietic stem cell transplant
MDS	myelodysplastic syndrome
MM	multiple myeloma
MPS	myeloproliferative syndrome
MR	minimal response
NHL	non-Hodgkin's lymphoma
OS	overall survival
PB	peripheral blood
PCR	polymerase chain reaction
PFS	progression-free survival
PR	partial remission
VOD	veno-occlusive disease

1. INTRODUCTION

Autologous transplantation of peripheral blood (PB) haematopoietic stem cells (HSCs) is a widely used strategy for recovery following high-dose chemotherapy in patients with haematolymphoid malignancies or solid tumours. Stem cells for transplantation are usually obtained from PB after treatment with chemotherapy with or without a cytokine (usually granulocyte colony stimulating factor [G-CSF]), or after treatment with a cytokine alone (such as G-CSF).

The Mozobil® (plerixafor) clinical development programme evaluated the use of plerixafor for stem cell mobilisation in oncology patients, and included patients undergoing mobilisation treatment for the first time as well as failed and predicted poor mobilisers. Due to the large proportion of autologous transplants represented by the lymphoma and multiple myeloma (MM) disease groups, the programme focused on establishing safety and efficacy of plerixafor in these patient populations, allowing evaluation in a homogeneous population with regards to the basic disease as recommended in the Committee for Proprietary Medicinal Products (CPMP) Points to Consider CPMP/EWP/197/99.

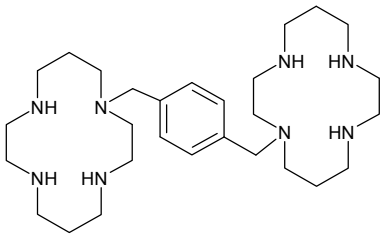
A marketing authorisation for the use of plerixafor in the European Union (EU) was issued on 31 July 2009. Mozobil® (plerixafor) is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly.

As a post-approval commitment to the European Medicines Agency (EMA), Genzyme will compare outcomes of progression-free survival (PFS), overall survival (OS), and relapse rate in transplant patients who receive plerixafor (+ G-CSF or + G-CSF + chemotherapy) for the mobilisation of PB CD34+ cells with patients who receive standard methods for mobilisation (i.e., G-CSF + chemotherapy or G-CSF alone). The source of data for this analysis will be the European Group for Blood and Marrow Transplantation (EBMT) registry. Data will be analysed at pre-specified time points as described in this document.

1.1. Background

Plerixafor is a haematopoietic stem cell (HSC) mobiliser with a chemical name l, 1'-[1,4-phenylenebis (methylene)]-bis-1,4,8,11- tetraazacyclotetradecane. It has the molecular formula $C_{28}H_{54}N_8$. The molecular weight of plerixafor is 502.79 g/mol. The structural formula is provided in Figure 1.

Figure 1: Structural Formula for Plerixafor



Plerixafor is a selective inhibitor of the chemokine receptor CXCR4, which is a member of the 7 transmembrane, G-protein-coupled, receptor family. Plerixafor is in a different pharmacotherapeutic class than other HSC mobilising agents and acts by binding to CXCR4, preventing the binding of its ligand SDF-1 and thereby inhibiting events downstream of SDF-1 including SDF-1-mediated G-protein activation, receptor internalisation, calcium flux, and chemotaxis (Hatse, 2002, *FEBS Lett*; Fricker, 2006, *Biochem Pharmacol*). Plerixafor does not cross-react with other chemokine receptors including CXCR7, for which SDF-1 is also a ligand. The SDF-1/CXCR4 interaction is an integral part of the mechanism of homing and retention of HSC in the bone marrow and inhibition of this interaction by plerixafor mobilises HSCs from the bone marrow (Fruehauf and Seeger, 2005, *Future Oncol;* Lapidot, 2005, *Blood*). Unlike cytokines used for HSC mobilisation (e.g., G-CSF), plerixafor is not a growth factor and does not cause cell proliferation or expansion. Additionally, although plerixafor may inhibit stromal cell interactions and anti-apoptotic signalling via the CXCR4/SDF1 axis, it is not cytotoxic as opposed to the chemotherapeutic agents used for HSC mobilisation. Therefore, plerixafor has a unique mechanism of action compared with other HSC mobilising agents (Nervi, 2006, *J Cell Biochem*; DiPersio, 2009, *Nat Rev Drug Discov*).

1.2. Rationale for Analysis of EBMT Registry Data

At the request of the EMA, the analysis of EBMT registry data for clinical outcomes including progression-free survival, overall survival, and relapse rate, is being undertaken to evaluate the long-term outcomes for patients who received plerixafor for stem cell mobilisation and haematopoietic stem cell transplantation (HSCT) compared with patients who received other mobilisation methods for HSCT. Since there is a theoretical risk of tumour cell mobilisation with any stem cell mobilisation method, the evaluation of these outcomes will provide the most relevant data to compare long-term effects of transplantation with cells mobilised by plerixafor versus transplantation with

cells mobilised by other methods. The analysis of data from a well established registry like the EBMT registry allows for follow-up of a large number of patients who are representative of the patient population receiving plerixafor.

The EBMT is a non-profit, scientific society representing 527 transplant centres in and outside Europe. The EBMT promotes all activity aiming to improve stem cell transplantation or cellular therapy, which includes registering all the activity relating to stem cell transplants. The data are entered, managed, and maintained in a central database with internet access; each EBMT centre is represented in this database. Centres can submit data either by entering it directly into the database or by sending MED-A and MED-B forms to the EBMT Data Office in Paris or their own national registry (Hewerdine, 2010, *Submitting Data to the EBMT)*. The EBMT reported that in 2007, 15,491 patients received their first autologous transplant. Of these, 12,981 were for haematological malignancies and lymphoproliferative disorders including MM, other plasma cell disorders, HD, and NHL (Gratwohl, 2009, *Bone Marrow Transplant*).

1.3. Clinical Findings and Review of the Literature Regarding Tumour Cell Mobilisation

The clinical relevance of tumour cell mobilisation and tumour cell contamination in the apheresis product is not clear. It is recognised that tumour cell contamination may occur during the mobilisation and collection of stem cells from patients with MM, lymphoma, and other cancers. Tumour cell mobilisation can occur following G-CSF mobilisation, as well as other mobilisation methods such as chemotherapy. In fact, there is a measurable increase of tumour cells into peripheral blood following standard chemotherapy and radiation treatments for cancer (Biswas, 2007, *J Clin Invest*). However, the detection of tumour cells is extremely difficult given the low number of tumour cells compared to normal cells and the large variety of potential tumour types. The sensitivity and specificity of the various tumour cell detection methods varies and is highly dependent on the method employed.

For the plerixafor programme, investigation of tumour cell contamination using tumour cell detection methods was conducted in patients with NHL and MM in four Phase 2 studies (AMD3100-2101, 2102, 2103, and EU21) and one Phase 3 study (AMD3100-3101). The assays used in these investigations included flow cytometry to detect myeloma cells on the basis of cell markers and DNA content (1 study), quantitative polymerase chain reaction (PCR) for Bcl-2 translocations (3 studies), and quantitative PCR for tumour-specific immunoglobulin VH CDR3 gene segments (1 study). The results showed that there was no mobilisation or very low levels of MM

or lymphoma cells observed in the blood or apheresis products of patients receiving plerixafor in these studies. Importantly, using the tumour-specific and highly sensitive CDR3 PCR technique in one study (Study AMD3100-EU21), mobilisation of tumour cells was observed following treatment with G-CSF alone at a level similar to that previously reported in the literature (Anagnostopoulos, 2004, *Bone Marrow Transplant;* 2007, *Amgen Inc. Neupogen® (filgrastim) Prescribing Information*); however, there was no significant increase in tumour cell mobilisation following plerixafor administration. In contrast, the relative number of CD34+ stem cells increases significantly compared to G-CSF alone. Given this data, any tumour cell contamination of the apheresis product following plerixafor administration would be expected to be similar or less than that following G-CSF mobilisation alone when the same number of CD34+ stem cells is collected.

Tumour Cell Mobilisation and Outcomes

Of critical importance is the relevance of tumour cell mobilisation to clinical outcome. It is possible that tumour cells (specifically the subset of tumour cells capable of initiating tumour growth) in the re-infused apheresis product could lead to re-establishment of a cancer. In the literature, clinical transplant studies have shown that low levels of tumour cell contamination of stem cell products have not affected clinical outcome, and that relapse may be caused by re-growth of residual tumour rather than by re-infusion of tumour cells in the apheresis product (Williams, 1996, *J Clin Oncol*; Stewart, 2001, *J Clin Oncol*; Bourhis, 2007, *Haematologica*). Therefore, plerixafor is not expected to cause significant mobilisation of MM or NHL cells and is not expected to negatively impact clinical outcome.

2. DESIGN AND OBJECTIVES

Study Design

This is an analysis of a prospectively-defined cohort of patients with data reported retrospectively to the EBMT who have lymphoma or MM and who have undergone first autologous HSC transplantation during the years 2008 up to and including 2011. For Lymphoma the data collection and analyses will be focused on the first autologous transplantation with PBSC. For MM it is necessary to collect all autologous PB transplantations because plerixafor is often used at a subsequent transplant.

Patients will be categorised by the method of stem cell mobilisation that was given prior to HSCT. The baseline characteristics of these treatment groups will be described with particular attention to specific predetermined factors, including pre-specified factors of prognostic importance.

Since the mobilisation treatment groups are likely to differ according to baseline characteristics, there is the potential for outcomes to be confounded by indication. To mitigate these differences, propensity score analysis will be conducted to identify study cohorts that are balanced with respect to baseline characteristics (see Section 5.1) Following the propensity score analysis, the outcomes for each mobilisation treatment group will be analysed.

Objectives

The objectives of the study are to compare PFS, OS, and relapse rate of patients with MM or lymphoma who have received autologous transplants of stem cells using cells mobilised with plerixafor + G-CSF to other mobilisation methods. The following mobilisation regimens will be compared:

- G-CSF + plerixafor to G-CSF alone
- G-CSF + plerixafor to G-CSF + chemotherapy
- G-CSF + plerixafor + chemotherapy to G-CSF + chemotherapy

Outcomes for patients with MM will be analysed separately from outcomes of patients with lymphoma.

3. STUDY TASKS, MILESTONES AND TIMELINES

This protocol describes the data retrieval and analysis of cohort data from established EBMT registry. Data will be retrieved from the registry for patients with date of transplant between 01 January 2008 (to capture data entered for patients in the Compassionate Use Programme) and 31 December 2011 (i.e., over a 4-year time period) eligible to be included in the analysis. Follow-up data on patients selected for the analyses will be collected from the EBMT registry from time of transplant up to 31 December 2014 (i.e., individual patients will have 3 years to 7 years of follow-up dependent on date of transplantation).

Recruitment of Subjects for Analyses:

Start of inclusion of patients (transplant date) – 01 Jan 2008

End of inclusion (last patient included, transplant date) – 31 Dec 2011

Follow-up period (allows 3 years of follow-up data on the last patient included):

End of follow up period – 31 Dec 2014

Data Collection, Analysis and Report:

Data collection completed – end second quarter 2015

Final analysis and report – third to fourth quarter of 2015

The statistical analysis of outcomes (PFS, OS, and relapse) will only be carried out at the end of the data collection period and will be provided in the Final Report.

The EBMT will collect the data in the course of established EBMT procedures (Hewerdine, 2010, *Submitting Data to the EBMT*). Regional regulatory reporting requirements on individual patient data will be followed by the physicians. Therefore, physicians are to notify the appropriate product manufacturers or regulatory authorities directly of adverse events potentially related to mobilisation agents or other drug exposures. The EBMT database only captures a limited number of transplant complications and does not include assessments of severity, outcome, or relatedness to any drug administered (see Appendix A for the solicited terms ["complications"] on the MED-B form).

4. DESCRIPTION OF THE RESEARCH METHODS

4.1. Population to be Studied

For inclusion in the cohort analysis, patients must have data in the EBMT registry that meet the following criteria:

- Adults diagnosed with lymphoma or MM
- Received first autologous transplants of PB non ex-vivo manipulated stem cells in the time period listed above using cells mobilised with one of the following regimens:
  - plerixafor plus G-CSF
  - plerixafor plus G-CSF plus chemotherapy
  - G-CSF alone or
  - G-CSF plus chemotherapy

Patients included in the plerixafor groups will be those treated according to the label.

For Lymphoma the data collection and analyses will be focused on the first autologous transplantation with PBSC. For MM it is necessary to collect all autologous PB transplantations since multiple transplants are often part of a standard care for these patients.

- Provision of informed consent (i.e., all patients with data in the EBMT registry will have signed consent at the time of transplantation for the potential use of their data for analysis)

4.2. Operational Definitions of Variables

Data will be retrieved from variables identified on the EBMT MED-B forms. A list of variables, codes, and definitions that will be included in the analyses are provided in Appendix A, EBMT MED-B POPULATION OR CONFOUNDERS Field Codes. Additional questions on whether patients are poor mobilisers will be added as a MED-C form (see Appendix B: Additional questions for CALM project).

The use of plerixafor off-label will be collected separately (see protocol MOZ19310),

4.3. Confounders

All data for potential confounding variables will be collected from the EBMT database for possible inclusion in the analysis. The table in Appendix C provides literature sources describing the biological plausibility of each confounder. Potential confounders include:

- Age, gender
- Disease type (MM, malignant lymphoma, and their subcategories)
- Bone marrow involvement
- Stage of disease at diagnosis
- Status of disease at collection (i.e., apheresis)
- Status of disease at conditioning (preparation for transplant) for MM*
- Status of disease at time of transplant (complete remission, partial remission, 1st relapse, 2nd relapse, duration of remission[s]) for Lymphoma*
- Conditioning regimen
- Number of extranodal sites (Hodgkin's Lymphoma and non Hodgkin's Lymphoma) at diagnosis
- Year of autologous stem cell transplantation)

* As the period between conditioning and transplantation is only ca. 7 days, just one staging per disease is given.

- Engraftment, including engraftment failure
- Interval from diagnosis to transplantation
- Performance status (Karnofsky) at transplant
- Centre
- Country
- Follicular Lymphoma International Prognostic Index (FLIPI) score (# nodal sites, LDH, age, Hb, Ann Arbor stage) at diagnosis
- Other variables to be determined (the literature will be searched periodically and this list of confounders will be updated as needed to reflect new information). This is possible only for the items that are collected on the MED B/C forms. No new items are to be added to the MED B/C form during the study period

The list of confounders will be finalised before outcome analyses are performed (see Statistical Analysis Plan).

5. STATISTICAL ANALYSIS

The overall goal of this protocol is to be able to compare outcome measures on MM or lymphoma patients who received autologous transplants of PB stem cells using cells mobilised with plerixafor + G-CSF to other mobilisation methods. The following mobilisation regimens will be compared:

- G-CSF + plerixafor (G + P) to G-CSF alone (G alone)
- G-CSF + plerixafor (G + P) to G-CSF + chemotherapy (G + C)
- G-CSF + plerixafor + chemotherapy (G + C + P) to G-CSF + chemotherapy (G + C)

Patients treated off-label will be excluded from the analysis. Analysis for MM and lymphoma patients will be performed separately. Within each disease, outcomes for patients treated with plerixafor will be compared to other treatment groups separately.

The analysis will be performed in 2 independent stages: patient identification and outcomes analysis.

Statistical assessment of the association of each confounder with plerixafor use or with outcome is described in the Statistical Analysis Plan. In addition, before statistical modelling begins, the completeness of all confounders will be assessed. If missing data are identified then a multiple imputation approach will be used in order to account for missing data. Complete data sets will be generated and used in the propensity score (patient identification) and outcome analyses. As an exploratory analysis, comparison groups other than those listed above may be considered.

5.1. Propensity Score Analysis: Patient Identification

In order to identify cohorts that are balanced with respect to baseline covariates, the propensity score technique will be used. Variables to be incorporated into the propensity score analysis will only consist of baseline (pre-treatment) information. No post-baseline or outcome information will be used in this step of the analyses. By using pre-treatment characteristics only in the propensity score modelling, the comparison groups can be formed independent of any outcome information. Thus, the models fit and diagnostics used to assess whether the analyses are successful in creating comparison groups will only include patient level data that was available prior to the initiation of therapy. This approach for model building will allow the exploration of several possible comparison group scenarios based upon different propensity score models, with the ultimate goal of choosing the analysis that optimises the total number of patients included in the comparison groups while minimizing any observed differences between groups on background, pre-treatment characteristics.

Genzyme will work with an independent statistical consultant to determine the best possible model to calculate propensity scores for patient identification. Once a propensity score model is fit then matched samples or stratified samples will be constructed and the success of the model will be assessed based on whether balance between the treated and control groups is achieved in either the matched or stratified samples.

Briefly, the propensity score approach will estimate the conditional probability of being treated by a particular regimen for each participant and then using the techniques described above (matching or stratification) groups of participants who received different treatments but had similar propensity scores will be identified. These groups (either matched groups or strata) will then be used in the outcome analyses as a way to control for potential imbalances that existed on pre-treatment characteristics.

5.2. Outcomes Analysis

There may be significant differences in pre-treatment risk factors among the 4 treatment groups and these differences may contribute to any observed differences in outcome measures. In order to control for the potential confounding due to pre-treatment risk factor imbalances among groups, propensity score analyses will be used to find comparable groups for analysis of outcomes as described in Section 5.1. Since it is not possible to identify *a priori* whether a matching (e.g., one-to-one or one-to-many) or stratification (e.g., quartiles or quintiles) approach will achieve the best balance, both modelling approaches will be considered during the patient identification stage. Based

on the final method that is chosen, the analysis of outcomes will be structured accordingly. In the case of matching patients according to propensity scores, the outcomes analysis will proceed assuming the matched cohorts are independent and the propensity score may be used as a covariate in the analysis. Plerixafor patients who are not included in the matched patient datasets from the propensity score analysis will have their data listed. The analysis will proceed using a stratified approach, where the propensity score will be used to stratify patients into similar categories (e.g., quartiles or quintiles based on the overall distribution of propensity scores).

Survival and progression/relapse will be measured from the date of first transplant to the date of death, progression/relapse or censor. For patients who have a subsequent transplant using cells from the same mobilization regimen, event durations will be measured from the date of the first transplant. In presence of a relevant proportion of patients who have subsequent transplants using cells from a different mobilization regimen, several approaches could be followed, including censoring at time of the subsequent transplant using cells from a different mobilization regimen.

Standard survival analysis techniques, including Cox proportional hazards with covariates as appropriate, will be used to generate point estimates and 95% confidence intervals comparing PFS and OS between the treatment groups (e.g., using the hazard ratio for the treatment effect, and 95% confidence interval, from the Cox model).

For the main analysis, relapse rate will be evaluated according to the EBMT criteria (cfr. EBMT Statistical Guidelines). For secondary purposes, it could also be evaluated as a proportion, with 95% confidence intervals, of patients reporting disease relapse for each year of follow-up and compared between treatment groups.

Relapse for patients in CR and PR will be analyzed separately.

Engraftment and complications of transplantation will be summarised descriptively by treatment group. Variables will include haematological recovery (time to absolute neutrophil count recovery [$\geq 0.5 \times 10^6$/L] and platelet reconstitution [platelets $\geq 20 \times 10^9$/L or $\geq 50 \times 10^9$/L]) and complications within 100 days after transplantation. Summaries of complications will include all infection-related complications and non-infection-related complications, if appropriate. Summaries of complications will not include assessments of causality, severity, and outcome because these are not captured in the EBMT database.

Size of the Sample

For this observational analysis of EBMT registry data, it is not possible to predetermine the number of patients who will meet the criteria to be included in the analysis.

However, the number of patients potentially available for analysis can be estimated based on the number of patients with lymphoma or MM likely to receive autologous transplantation in Europe over the 4 years of the study. Overall, it is estimated that approximately 4,800 patients would potentially be available for inclusion in the analyses: approximately 400 treated with G-CSF alone, 200 treated with G-CSF + plerixafor, 2,800 treated with G-CSF + chemotherapy, and 1,400 treated with G-CSF + plerixafor + chemotherapy. These estimates are based on an average of approximately 11,500 autologous transplants per year for lymphoma or MM being included in the EBMT registry over the 4 years of the study and the assumptions that (1) 85% of transplants use cells mobilised by G-CSF + chemotherapy and 15% use cells mobilised by G-CSF alone, (2) 15% of patients transplanted with each regimen (G + C, G-alone) are treated with plerixafor, (3) plerixafor is available in all centres and 30% of MED-B forms would be fully completed, (4) 70% of plerixafor-treated patients complete the Med B form and are matched at a 1:2 rate (plerixafor : control) comparator patients.
The actual number of patients included in the analyses will depend on accrual, completeness of data reporting, and the results of propensity scoring (see Section 5.1 and the Statistical Analysis Plan).

6. PLANS FOR PROTECTING HUMAN SUBJECTS

Patients will have existing signed informed consent for anonymised data to be held by EBMT and used in analysis. This is the responsibility of the principle investigator at the institute. Informed consent forms are to be kept at the centre.

7. PLANS FOR COMMUNICATING STUDY RESULTS

EBMT will provide regular reports on accrual information. Genzyme will include this information in the Periodic Safety Update Reports (PSURs) to cover the 4-year time period during which patients with transplants in the registry are eligible to be considered for the analysis (i.e., 01 January 2008 to 31 December 2011). The final analysis report will be submitted to the Authorities as per agreement. Any external publication of data derived from the cohort analyses described in this protocol will conform to the Authorship Guidelines for EBMT Publications (http://www.ebmt.org/).

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APPENDIX A, EBMT MED-B POPULATION OR CONFOUNDERS FIELD CODES

Table A-1. EBMT MED-A and MED-B Field Codes and Definitions to be Used in Analysis (Identity of Patient Populations or Potential Confounders)

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
EBMT Centre Code	**CENTRE Med A and B; also on Med A annual post transplant form**	Every transplant centre on submitting data to the EBMT receives a CIC which should be entered here. An anonymous number is provided to Genzyme
Date of Birth	**DATPATBD Med A and B; also on Med A annual post transplant form**	Write the date of birth of the patient. If you do not know the exact date, apply the following: If you know the month and year but not the day, use "01" as day; If you do not know the month, use "01" (January) as month. Try to obtain exact dates as much as possible since they are crucial in identifying the registration when adding follow up data. Date of birth will be recoded to age at transplant and provided to Genzyme
Sex (male/female)	**PATSEX Med A and B; also on Med A annual post transplant form**	Indicate the gender of the patient.
Date of initial diagnosis	**IDAABB Med A and B**	Write down the date of diagnosis of the disease for which the patient is being transplanted. If the disease is of secondary origin, write the date of diagnosis of the disease of secondary origin, not the date of diagnosis of the original disease. NOTE: Remember that an acute leukaemia preceded by a myelodysplastic or myeloproliferative syndrome (MDS or MPS) is not a secondary disease, but rather a final stage of the myeloid syndromes. In this case, the date of diagnosis is the date of the MDS or MPS. If there is a concurrent disease (autoimmune disease, for example) for which the procedure is also indicated, add another date of diagnosis and indicate to which disease it applies.
Primary disease diagnosis	**DISMCLFD Med A Disease classification sheet and Med B general form**	The Med-A contains 12 Disease classification sheets. Select the one that contains the diagnosis the transplant was indicated for and fill in the relevant boxes. To fill these sheets correctly, please go to the Disease subclassification sections of this manual relevant to each main diagnosis.
Non-Hodgkin's lymphoma or Hodgkins (checkbox) Note: there is a list of NHL types under NHL B-Cell neoplasms with	**VREALCLS Med A disease classification sheet and Med B general form**	This classification refers to the different sub-groups of NHL. It reflects the main type of lymphocytes involved (B or T) and the cellular level of malignant transformation. The B-cell lymphomas are on the left of the page, and T- and NK-cell lymphomas on the right. The exact diagnosis has to be given in the pretransplantation letter or in the description given by the

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
checkboxes next to each one (e.g. follicular lymphoma [Grade 1, II, EE, and unknown], mantle cell lymphoma, extranodal marginal zone of MALT type, etc)		pathologist. The description can be found in the patient's file, either in referral letters, in the medical notes, or in the pathology report. If you have any problems finding this information, or are unsure on how to code it, please ask the treating physician. This is important information and should not be left blank. The WHO subclassification was preceded by the REAL, KIEL and Working Formulation classifications. It is possible that the information recorded in the notes of the patients who were diagnosed some years ago follow these earlier classifications. It is possible, given sufficient information, to equate the old classification to the current one as described below, but it is not easy. If you are unsure please ask the treating physician to interpret the classifications for you. If the patient's diagnosis is Hodgkin's lymphoma, please tick the appropriate box. If the patient has a lymphoma like malignancy, but you can't find the specific type in the available list, please tick Other and provide a full description.
Stage at diagnosis (Stage I-III; unknown Med form B also included not evaluated, Systemic symptoms of absent, present, not evaluated or unknown	**VSTGDST** **Med A and B** **disease specific** **VBSYMPTO** **Med A and B** **disease specific**	*Ann Arbor staging* **Stage I** one area of lymph nodes is affected. It includes: stage Ie: localised involvement of one non-lymphatic organ **Stage II** two or more areas of lymph nodes on the same side of the diaphragm are affected **Stage IIe**: one or more areas of lymph nodes on the same side of the diaphragm are affected PLUS localised involvement of one or more non-lymphatic organs on the same side of the diaphragm **Stage III** groups of lymph nodes on both sides of the diaphragm have been affected. It includes: **Stage IIIe**: groups of lymph nodes on both sides of the diaphragm have been affected PLUS one localised involvement of one non-lymphatic organ **Stage IIIs:** groups of lymph nodes on both sides of the diaphragm have been affected PLUS the spleen **Systemic symptoms** Systemic symptoms are: night sweats, weight loss (more than 10% of body weight in 6 months), fever > 38C not caused by other diseases. Tick box A if there are no symptoms. Tick box B if any of these symptoms are present. The information will be in the patients file.
Date of HSCT	**IDAABC / IDAABE** **Med A and B; also on Med A annual follow-up**	Day 0 is considered the day of the first haematopoietic stem cell infusion if there are multiple infusions of one or several graft products over several days after the same conditioning regimen.

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
Classification for plasma cell disorders including MM	**VPLCEDS1 Med A disease classification and Med B disease specific information**	This information is to be found in the patient's file. **Multiple myeloma** (MM; synonyms: 'Myeloma', 'myelomatosis') is a lymphoproliferative malignant haematological disease arising from malignant plasma cells and B-lymphocytes. The malignant cells usually produce a monoclonal immunoglobulin readily identifiable in plasma (M-component) or urine (Bence Jones' protein or urinary light chains). The most typical feature for MM is skeletal damage with lytic bone lesions and generalised osteopenia. Other common features are various cytopenias, polyclonal hypogammaglobulinemia, renal failure and polyneuropathy
Subclassification for MM	**VPLCEDS2**	**IgG-IgA-IgD-IgM-IgE**: Indicates the heavy chain type of the M-component (= monoclonal protein = monoclonal immunoglobulin = monoclonal Ig) in "common" type myeloma. Should be left blank in non-secretory and light chain myeloma. In most cases there is only one type of M-component but in some very rare cases, two of them, IgG and IgA for example, may appear simultaneously in serum/plasma.
Subclassification for MM	**VPLCEDS3 Med A disease classification and Med B disease specific information**	**Common type** myeloma means the most usual form, with a complete monoclonal immunoglobulin (M-component) of usually IgG- or IgA-type, rarely IgM, very rarely IgD, and on extremely rare occasions IgE, in serum/plasma. • **Light chain** is synonymous to 'Bence Jones myeloma', and is a myeloma where the monoclonal protein is found in the urine as light chains of kappa or lambda type. • **Non-secretory** (synonym: non-producing) is a subclass where no monoclonal protein can be found either in blood or urine; diagnosis is by bone marrow sample.
Subclassification for MM	**VPLCEDS4 Med A disease classification and Med B disease specific information**	**Kappa-Lambda**: Indicates the type of light chain of the M-component (e.g. IgG-kappa, IgG-lambda etc) in 'common type' myeloma or the type of light chains in urine in light chain myeloma. Should be checked for 'common' and light chain, left blank for non-secretory.
Conditioning	**VCHEMOTH Med A disease classification and Med B disease specific information**	Drugs *(agents)* This information is crucial. Write down here all the agents be them chemotherapy, antibodies, hormones, etc. which are administered to the patient as part of the preparative regimen. They must all have been given before the actual date of cell infusion (HSCT date or Day 0).
FLIPI items related to diagnosis, like # nodal sites, Hb, LDH, Ann Arbor staging	**Med B disease specific information**	At diagnosis of follicular lymphoma, using the standard haematological items, clinical items from MED B

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
Subclassification for MM	**VSALMDUR Med A disease classification and Med B disease specific information**	**STAGE AT DIAGNOSIS (Salmon and Durie); (ISS)** Data to be found in patient files. Staging is the clinical classification of the severity of the disease at the time of Diagnosis. In MED-A, please complete the Salmon & Durie staging. In MED-B, please complete both the Salmon and Durie and ISS staging. Salmon and Durie is defined as follows: **Stage I**: Haemoglobin > 9.9 g/dL plus Serum-calcium < 2.65 mmol/L plus No lytic lesions or one single minor lesion plus Monoclonal IgG < 50 g/L or monoclonal IgA < 30 g/L (for 'common type' myeloma) or light chains in urine < 4 g/24 hours (for light chain myeloma). **Stage II**: Not fulfilling criteria for stage I or Stage III. **Stage III**: Haemoglobin < 8.5 g/dL and/or Serum-calcium > 2.65 mmol/L and/or Monoclonal IgG > 70 g/L or monoclonal IgA > 50 g/L ('common' type) or light chains in urine > 12 g/24 hours and/or Multiple skeletal lesions and/or pathologic fracture(s). ISS (International Staging System) is defined as follows: **Stage I**: Serum β2-microglobulin < 3.5 mg/L and serum albumin ≥ 35 g/L. **Stage II**: Not fulfilling criteria for stage I or stage III. **Stage III**: Serum β2-microglobulin ≥ 5.5 mg/L.
Lymphoma Status at HSCT Choices are CR, never treated, primary refractory disease, very good 1st PR, 1st PR	**VDISESTA Med A disease classification and Med B disease specific information**	Indicate the number of the CRs this patient has had including the present one. Indicate also whether the CR was confirmed: **CR confirmed:** There are no abnormalities detected in the scan except if there is previous history of a positive PET scan. In this case, a negative PET can be taken as confirmation of Complete remission even in the presence of abnormalities in the CT scan. **CR unconfirmed:** There are scan abnormalities of unknown significance (in the absence of progression this will finally mean cure). **Untreated (untested) relapse**: No further treatment has been given from the date of relapse. **Sensitive (responding) relapse**: The patient received another treatment after relapse and achieved a PR (see earlier definition). **Resistant relapse:** The patient received another treatment following relapse but PR was not achieved. **If no CR achieved**, choose: **Never treated** (at diagnosis, untreated): The patient has never been treated for this disease. **Primary refractory disease (PIF):** The patient has never obtained a complete or partial remission. **Very good 1st PR**: A reduction in disease of >90% **1st PR**: A reduction in disease of >50%
MM Status at Conditioning	**VDISESTA Med A disease**	**Response**: Very important! Please, always fill this part. The EBMT-CIBMTR response definitions are applied, as

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
Choices are sCR, CR, VGPR, PR, no change, and progression.	**classification and Med B disease specific information**	follows: **sCR (stringent complete remission):** All of the following: - CR as defined below - Normal free light chain ratio - Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence **CR (complete remission):** All of the following: - Absence of detectable monoclonal immunoglobulin in serum or monoclonal light chains in the urine by immunofixation. Detectable monoclonal immunoglobulin, even if impossible to quantify, is not a CR. - <5% of plasma cells in bone marrow aspirate - No increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory) **VGPR (very good partial remission):** One or more of the following: - Serum and urine M-protein detectable by immunofixation but not on electrophoresis - >90% reduction in serum M-protein plus urine M-protein level <0.1g/ per 24h In addition, there must be no increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory) **PR (partial remission):** All of the following: - >50% reduction in serum M-protein plus reduction in 24h urinary M-protein by >90% or to <0.2g/ per 24h In the absence of measurable serum and urine M-protein, the following criteria applies: - A decrease in the difference between involved and uninvolved free light chain (FLC) of more than 50% If the FLC assay cannot be measured, the following criteria applies: ▪ >50% reduction in plasma cells provided baseline bone marrow plasma cell percentage was >30% - No increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory) **Stable disease**: - Does not meet the criteria for CR, VGPR, PR or progressive disease (includes the old Minimal response (MR) criteria) **Progression**: One or more of the following: - Increase of 25% or more in measurable monoclonal immunoglobulin in serum or urine (absolute increase must be >0.5g/dL) - Increase of 25% or more in urinary light chains (absolute increase must be >0.2g/ per 24h) In the absence of measurable serum and urine M-protein, the following criteria applies: ▪ An increase of 25% or more in the difference between

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
		involved and uninvolved free light chain (absolute increase must be >0.01g/dL) - An increase of 25% or more in bone marrow plasma cells (absolute % must be >10%) - Increase of old/appearance of new osteolytic bone lesions on x-ray - Appearance of soft tissue plasmacytoma - Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell disorder
Performance score **SCORE** □ 100 (Normal, NED) **KARNOFSKY** □ 90 (Normal activity) □ 80 (Normal with effort) □ 70 (Cares for self) □ 60 (Requires occasional assistance) □ 50 (Requires assistance) □ 40 (Disabled) □ 30 (Severely disabled) □ 20 (Very sick) □ 10 (Moribund) □ Not evaluated □ Unknown	**KARNOFSK** **Med A and B**	The Karnofsky and Lansky are standard performance scales used to measure the well being of a patient. The Karnosfsky is used in adults and the Lansky is used in paediatrics. These scores are frequently integral to risk indexes and it is important that they be provided. Their measurement should be done prospectively, in the presence of the patient, since they are difficult to assess from the patient notes. The scales can be found in Appendix I of the manual. PF score at transplantation
Weight and height	**WEIGHTB** **VBQM** **Med B**	Weight (kg): ..... Height (cm): ..... The values should represent the situation at start of conditioning. At Transplant
Source of stem cells □ Peripheral blood	**VPBSC** **Med A and B**	For autograft, reinfused stem cells (SC) are obtained from the patient himself. The SC source may only be **VPBSC** - peripheral blood (PB) - for that patient, a "PB collection" has been performed in the past, throughout the aphaeresis procedure; each procedure could consist of 1 or more sessions.
Mobilisation date and number of mobilisation courses	**MOBDATE and NMBMOB** **Med B** **Autograft form**	Peripheral Blood: Total number of mobilisation courses To collect PBSC, the patient is submitted to a "mobilisation" course, consisting of chemotherapy followed by growth factor. In some cases, mobilisation may be performed only with the growth factor, or even – very rare- with only chemotherapy. After a given number of days from the administration of the drugs, the number of stem cells in the patient rises to a number that allows their collection. This is the procedure called "pheresis". According to the number of stem cells in the PB of each patient, a different number of sessions of pheresis may be needed. A "Course" is intended as one procedure starting form the mobilisation to the last pheresis performed. If, after one course, possibly consisting of several pheresis, a sufficient number of stem cells has not been obtained, the patient may be submitted to a second course. This is the

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
		information requested in the Total number of mobilisation courses field.
Collection (Harvest)	**IDAABC VCHEMOTH Med form B Autograft form**	**PERIPHERAL BLOOD MOBILISATION** *List all drugs: chemotherapy, growth factors, antibodies, etc.* For each mobilisation course, fill in: **IDAABC** Date of 1st pheresis: the date of the first pheresis performed for this mobilisation course. Number of this mobilisation: for this patient for this transplant **VCHEMOTH** Drug(s): the name(s) of the any drug(s) (chemo, growth factors, antibodies, etc.) used for mobilisation HSCT
Status at Collection (Choices are sCR, CR, VGPR, PR, no change and progression, relapse from CR)	**VDISESTA Med A disease classification and Med B disease specific information**	**Response**: Very important! Please, always fill this part. The EBMT-CIBMTR response definitions are applied, as follows: **sCR (stringent complete remission):** All of the following: - CR as defined below - normal free light chain ratio - Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence **CR (complete remission):** All of the following: - Absence of detectable monoclonal immunoglobulin in serum or monoclonal light chains in the urine by immunofixation. Detectable monoclonal immunoglobulin, even if impossible to quantify, is not a CR. - <5% of plasma cells in bone marrow aspirate - No increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory) **VGPR (very good partial remission):** One or more of the following: - Serum and urine M-protein detectable by immunofixation but not on electrophoresis - >90% reduction in serum M-protein plus urine M-protein level <0.1g/ per 24h In addition, there must be no increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory) **PR (partial remission):** All of the following: - >50% reduction in serum M-protein plus reduction in 24h urinary M-protein by >90% or to <0.2g/ per 24h In the absence of measurable serum and urine M-protein, the following criteria applies: - A decrease in the difference between involved and uninvolved free light chain (FLC) of more than 50% If the FLC assay cannot be measured, the following criteria applies: ▪ >50% reduction in plasma cells provided baseline bone marrow plasma cell percentage was >30% - No increase in size or number of lytic lesions if assessed

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
		(radiographic studies are not mandatory) **Stable disease**: - Does not meet the criteria for CR, VGPR, PR or progressive disease (includes the old Minimal response (MR) criteria) **Progression**: One or more of the following: - Increase of 25% or more in measurable monoclonal immunoglobulin in serum or urine (absolute increase must be >0.5g/dL) - Increase of 25% or more in urinary light chains (absolute increase must be >0.2g/ per 24h) In the absence of measurable serum and urine M-protein, the following criteria applies: ▪ An increase of 25% or more in the difference between involved and uninvolved free light chain (absolute increase must be >0.01g/dL) - An increase of 25% or more in bone marrow plasma cells (absolute % must be >10%) - Increase of old/appearance of new osteolytic bone lesions on x-ray - Appearance of soft tissue plasmacytoma - Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell disorder **Relapse from CR**: One or more of the following: - Reappearance of measurable monoclonal immunoglobulin in serum or urine by immunofixation or electrophoresis - Appearance of more than 5% plasma cells in the bone marrow - Increase of old/appearance of new osteolytic bone lesions on x-ray - Appearance of soft tissue plasmacytoma
Chronological no. of HSCT for this patient	**BMTNR Med A and Med B (autograft form)**	If number > 1: date of previous HSCT and type of previous HSCT (checkbox for allo or auto)
HSCT part of a planned multiple graft protocol? (no/yes)	**VMULGRAF Med A and B (med a y/n; more information on med b)**	Sometimes patients are entered into protocols which include more than one transplant. A typical example might be the use of an autologous transplant to prepare the patients for a non-myeloablative *(reduce intensity)* allograft. In this case the allograft would be number 2 out of 2 pre-programmed transplants. An autologous transplant form should have been completed for the first transplant. Some patients may have received a transplant (autologous or allogeneic) prior to this procedure as part of earlier management. In this case the current transplant is not part of a multiple graft programme.

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
		It is unlikely that we are dealing with a multiple graft program if more than 12 months have elapsed between the two transplants. A subsequent transplant that has been programmed to happen only if an intermediate event takes place (i.e., relapse) should not be considered part of a multiple transplant program.
Engraftment Check boxes for: Engraftment (see row below for additional fields to be filled out). No engraftment (with date of last assessment) and Lost graft (with date of graft failure)	**ENGRAF** **Med B only**	Engraftment means that the stem cells infused have been taken up by the patient's bone marrow ("have engrafted"). The first sign is an increase of neutrophils. Engraftment is considered to take place when the number of neutrophils in the patient's peripheral blood rises above 0.5 x 106/litre before additional treatment to obtain grafting is given. In an autologous transplant, chimaerism cannot be used to detect engraftment since it is the patient's own cells that engraft. No engraftment; is when neutrophils never reach ≥ 0.5 x 10^9/L. Lost graft: is if neutrophils increase to ≥ 0.5 x 109/L for at least two consecutive days and subsequently decrease to a low level until additional treatment to obtain engraftment is given.
Haemopoietic reconstitution (first of 3 consecutive days): Neutrophils Platelets > 20 x 109/L reached Platelets >50 x 10 9 reached	**DATRCGR2** **DPLAT50** **VPLAT20** **Med A and B**	Check boxes for each (yes, no, never below this level) with date if yes was checked)
Treatment for failure	**TRTGRFAI** **Med B only**	If the graft fails various treatments may be given. The most common is to give cytokines, which may or may not improve the graft performance. Therapy may be given to treat possible underlying causes of graft failure e.g. graft versus host disease (GvHD), infection. Permanent graft failure will cause the death of the patient and so often the patient receives further stem cells. The patient may be rescued by receiving an infusion of cryopreserved autologous stem cells. without any additional treatment being given to the patient, i.e. a 'top-up'. In other circumstances the patients may have been thought to have rejected the graft and so further conditioning with chemotherapy or immunotherapy might be given before the infusion of additional stem cells. This would be classified as a new transplant and a new set of MED B forms should be completed.
Complications within the first 100 days: Infection (no/yes)	**VCOMB100** **Med B only**	If "yes" please find explanations in the "INFECTION RELATED COMPLICATIONS" section of this manual.
Non infectious complications	**VOTCO100** **Med B only**	(check all that are applicable and supply dates: choices are idiopathic pneumonia syndrome, veno-occlusive disease (VOD), Epstein-Barr Virus (EBV) lymphoproliferative

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
		disease, haemorrhagic cystitis non infectious, acute respiratory distress syndrome (ARDS) non infectious, multiorgan failure non infectious, transplant-associated microangiopathy, renal failure requiring dialysis, other)
Date of last contact	**IDAABE**	This should be the last date the patient was known to be alive, not necessarily the last date the patient visited the clinic; for example, the patient may have phoned or has been met in the street. If the patient has died, it should be the date of death
Late graft failure (yes/no)	**LGRAFTL** **Med A annual follow-up**	For autografts you should interpret this question as to whether there has been a late graft loss. In this case, you should only fill Aplasia (=graft lost)
Did a secondary malignancy lymphoproliferative or myeloproliferative disorder occur? (yes/no; if yes provide date and diagnosis)	**IDAABB (yes/no)** **IDAABE (date/diagnosis)** **Med A annual follow-up**	Patients can develop secondary disorders like MDS, acute leukemia, or lymphoproliferative disorders. If this is the case, tick "Yes", provide date of diagnosis and indicate which diagnosis. This must be a disease for which the patient had not been diagnosed before the transplant.
Additional treatment	**VADDTREA** **Med A annual follow-up**	Indicate if the patient had additional treatment for the original condition or complications derived from the transplant. If yes: additional cell infusion (yes/no)
First relapse or progression after HSCT (yes, no, continuous progression since HSCT)	**VRELPROG** **Med A annual follow-up**	The relapse / progression status of the patient is one of the most important parameters in the data collection. Always use the latest possible dates for reference, even if you are using the "100 days after HSCT" form. So, for example, if you are filling in the MED-AB forms 1 year after transplant and you know that the patient relapsed 5 months after transplant, do not say “No” to the question “RELAPSE OR PROGRESSION**”,** write “Yes” and provide the exact date of relapse / progression even if this is after the 100 days. For all diseases, a relapse or progression indicates that there is a return of the original disease, which is **clearly** progressing as compared to the state of the disease prior to transplant. Because of the different diseases, more specific indications for diagnosing relapse or progression cannot be given here. Please look for it in the appropriate section of this manual. **1st Relapse:** Relapse means the occurrence of new sites of disease, or the re-occurrence of disease or systemic symptoms (B symptoms) after having achieved a complete remission which lasted for 3 months or more. It is called *progression* if complete remission lasted less than 3 months. Progression also describes any worsening of the disease status in patients previously assessed as not in CR. 1st relapse: means the first relapse that occurs after a first CR has been achieved. If CR was never achieved, you can skip this question, but

Form/Field	Code/ Found on Med A or Med B forms	Definition/directions from Med Forms A-B Manual
		make sure you marked "No" under "CR achieved" above. If CR was achieved and there was no 1st relapse, mark "No". If the patient has never had a CR, the status of the disease cannot be relapse.
Conception	**VCONCEPT**	Has patient or partner become pregnant after this transplant? Indicate whether a female patient or the partner of a male patient has become pregnant since the patient underwent the transplant procedure.
Survival status (alive/dead/lost to follow-up)	**VPATSTAT** **Med A and Med A annual follow-up**	Provide the most recent information you have. For example, if you are filling in the MED-AB forms 5 months after transplant and you know that the patient is dead now but was alive at 100 days, do not answer Alive, but Dead. The status must be the status at the Date of last contact and the latter must be either the very last date the patient was known to be alive or the date of death if the patient is known to have died.
Main cause of death	**VCAUSDTH**	The information on cause of death is very important. Tick only one major cause of death. If the death is transplant related, check as many causes as are considered to have been contributory to the outcome. Please check with your physician since this information is sometimes difficult to find in the patient's file. In the absence of clinical disease, a death caused by complications or infections after transplant is considered Transplantation related. In the presence of clinical disease, if the disease is progressing, the death will be considered as Relapse or progression, even if there are complications or infections during the post transplant period. However, if the disease was stable, or there had been an improvement after transplant, and the patient were to die of complications or infections, the death would be considered Treatment related. Relapse or progression Secondary malignancy Unknown Other Transplantation related cause : ***HSCT related cause (check as many as appropriate)*** GvHD Rejection/poor graft function Pulmonary toxicity Post transplant lymphoproliferative disorder Cardiac toxicity Infection Veno occlusive disorder Other

APPENDIX B. ADDITIONAL QUESTIONS FOR CALM STUDY

Additional Questionnaire (MED C)

CALM study

Inclusion period: 01/01/2008 to 31/12/2011

PATIENT REGISTRATION FORM

INCLUSION CRITERIA CALM STUDY

Disease Diagnosis ☐ Lymphoma

☐ Non Hodgkin Lymphoma (NHL)

Mature B-cell neoplasm

- ☐ Follicular lymphoma
  Grade ☐ I ☐ II ☐ III ☐ Not evaluated ☐ Unknown
- ☐ Mantle cell lymphoma
- ☐ Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT-lymphoma)
- ☐ Diffuse large B-cell lymphoma
  - ☐ Intravascular
  - ☐ Mediastinal
  - ☐ Primary effussion
- ☐ Burkitt lymphoma
  - ☐ High grade B-cell lymphoma, Burkitt-like *(provisional entity)*
- ☐ Lymphoplasmacytic lymphoma
- ☐ Waldenstrom macroglobulinaemia
- ☐ Splenic marginal zone lymphoma
- ☐ Nodal marginal zone B-cell lymphoma
- ☐ Primary CNS lymphoma
- ☐ Other B-cell, specify _____

Mature T-cell and NK-cell neoplasms

- ☐ Angioimmunoblastic T-cell lymphoma (AILD)
- ☐ Peripheral T-cell lymphoma, all types
- ☐ Anaplastic large cell, T/null cell, primary cutaneous
- ☐ Anaplastic large cell, T/null cell, primary systemic
- ☐ Extranodal NK/T cell lymphoma, nasal type
- ☐ Enteropathy type T-cell lymphoma
- ☐ Hepatosplenic gamma-delta T-cell lymphoma
- ☐ Subcutaneous panniculitis-like T-cell lymphoma
- ☐ Adult T-cell lymphoma/leukaemia (HTLV1+)
- ☐ Aggressive NK-cell leukaemia
- ☐ Large T-cell granular lymphocytic lymphoma
- ☐ Mycosis fungoides
- ☐ Sezary Syndrome
- ☐ Other T/NK-cell, specify _____

Transformed from another disease or another type of lymphoma

☐ No ☐ Yes ☐ Unknown

☐ Hodgkin Lymphoma

- ☐ Nodular lymphocyte predominant
- ☐ Lymphocyte rich
- ☐ Nodular sclerosis
- ☐ Mixed cellularity
- ☐ Lymphoma depleted
- ☐ Other, specify _____

☐ **Other Lymphoma, specify** _____

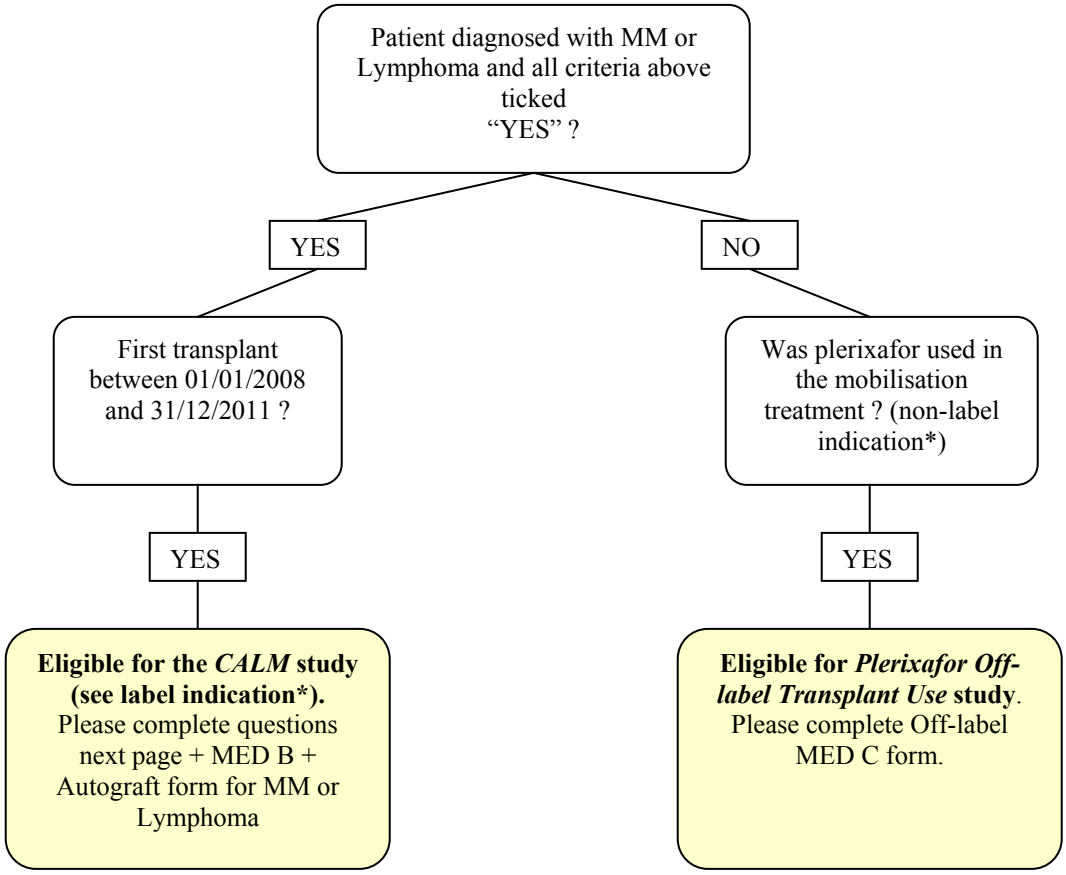
Disease Diagnosis ☐ MM

Classification	IG CHAIN TYPE	LIGHT CHAIN TYPE	SALMON & DURIE STAGE AT DIAGNOSIS
☐ Multiple myeloma	IgG	☐ Kappa	*(Multiple Myeloma only)*
☐ Multiple myeloma	IgA	☐ Lambda	☐ I and ☐ A
☐ Multiple myeloma	IgD		☐ II ☐ B
☐ Multiple myeloma	IgE		☐ III
☐ Multiple myeloma	IgM *(not Waldenstrom)*		
☐ Multiple myeloma-light chain only			
☐ Multiple myeloma-non-secretory			

Patient is ≥ 18 years at day of first transplant ☐ yes ☐ no

Patient received first auto PBSC transplant using cells with one of the following mobilisation regimens (please mark the one applicable): ☐ yes ☐ no

- ☐ G-CSF alone
- ☐ G-CSF + chemotherapy
- ☐ **Plerixafor + G-CSF**
- ☐ **Plerixafor + G-CSF** + chemotherapy



Label indication: Plerixafor is indicated in combination with G-CSF to enhance mobilisation of haematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with lymphoma and multiple myeloma whose cells mobilise poorly

TEAM

CIC I__I I__I I__I Hospital name _____

Contact person: _____

Date of this report ...../...../.....
yyyy mm dd

PATIENT

Unique Identification Code (UIC) _____ *(to be entered only if patient previouslyreported)*

Hospital Unique Patient Number _____

Date of birth...../...../.....
yyyy mm dd

Date of HSCT: ...../...../.....
yyyy mm dd

ADDITIONAL QUESTIONS

Patient is a proven poor mobiliser: ☐ no ☐ yes

If yes

In a previous mobilisation attempt, patient has failed to mobilise sufficient CD34+ cells in the peripheral blood to proceed to apheresis

☐ no ☐ yes

Please record the CD34+ cell count used in this decision:

_____ CD34+ cells/ul

In a previous mobilisation attempt, patient failed to collect sufficient cells to be able to proceed to transplantation

☐ no ☐ yes

In the current mobilisation attempt, peripheral blood CD34+ cell levels have failed to rise sufficiently at the predicted time for peak mobilization

☐ no ☐ yes

Please record the CD34+ cell count used in this decision: _____ CD34+ cells/ul

Patient is a predicted poor mobiliser ☐ no ☐ yes

If yes (please check all that apply)

Reasons ☐ Prior irradiation to marrow-bearing areas
☐ High exposure to marrow-damaging chemotherapy (e.g., drug type, number of cycles, and/or number of regimens)
☐ Other, ……..

If available, please record the pre-apheresis peripheral blood CD34+ level:

_____ cells/ ul

Patient is NOT a poor mobiliser: ☐ no ☐ yes

*N.B. In case plerixafor is used, please use the **off-label study form**!(the use of plerixafor in patients who are **NOT poor mobilisers** is considered off- label use) .*

PBSC mobilisation course

Bone marrow involvement at start of mobilisation regimen ☐ no ☐ yes

Blood volume processed _____

☝ ONLY IF FIRST AUTOLOGOUS TRANSPLANT WAS FOR LYMPHOMA

AT DIAGNOSIS:

Hb *(g/dL)* .... , ... ☐ Not evaluated ☐ Unknown

STATUS OF DISEASE AT COLLECTION

IMMEDIATELY PRIOR TO MOBILISING CHEMOTHERAPY AND/OR GROWTH FACTOR IF USED

If patient has <u>ever</u> achieved Complete remission

☐ Complete remission (CR)
- ☐ Unconfirmed
- ☐ Confirmed: ☐ By CT scan ☐ By PET

NUMBER OF THIS REMISSION
☐ 1st ☐ 2nd ☐ 3rd or higher

☐ Relapse

NUMBER OF THIS RELAPSE
☐ 1st ☐ 2nd ☐ 3rd or higher

TYPE OF RELAPSE
☐ Untreated (untested) ☐ Sensitive (responding) ☐ Resistant

If patient has <u>never</u> achieved a Complete remission

☐ Stable disease
☐ Primary refractory disease
☐ Very good 1st PR (> 90 %)
☐ PR

NUMBER OF THIS PR
☐ 1st ☐ 2nd ☐ 3rd or higher

☐ Progression

2nd HSCT? ☐ no ☐ yes, date ...../...../.....
yyyy mm dd

Plerixafor used for mobilisation at 2nd HSCT ☐ no ☐ yes

Did relapse occur after 2nd HSCT? ☐ no ☐ yes, date ...../...../.....
yyyy mm dd

APPENDIX C. POTENTIAL CONFOUNDERS LITERATURE SEARCH

Potential Confounder	Population (MM or NHL)	References
Affecting Outcome:		
Age	NHL	Ruiz-Soto_2005
	both	Lazarus_2008, Majolino_1999
	NHL	Vose_2004
Gender	NHL	Hosing, 2008
Weight	NHL	Tarella_2000
Disease Status: CR vs non-CR	both	Lazarus_2008, Won_2006, Vose_2004, Hosing_2008, Majolino_1999, Salar_2001, Yang_2009
Relapse vs Plateau	MM	Dingli_2006
Number of disease recurrences	NHL	Ruiz-Soto_2005
Disease stage (I-IV) / Disease Histology (type of disease)	both	Vose_2008
Poor performance status	NHL	Won_2006
Karnofsky performance score	NHL	Lazarus_2008
Duration from diagnosis to transplant	both	Lazarus_2008, Vose_2004 / Bensinger_1996
Prior treatment		
Chemotherapy	MM	Bensinger_1996
Prior radiotherapy	MM	Bensinger_1996
Chemo vs Chemo+TBI	NHL	Salar_2001
Interval from diagnosis to first relapse before transplantation	NHL	Vose_2004
Genetic risk factors (t(4;14) / t(11:14) / p53 deletions and other)	MM	Chang_2005, Dingli_2006, Vangsted_2009
LDH level (normal vs. increased)	both	Vose_2004, Hosing_2008 / Rajkumar_2001
Circulating myeloma cells (CMC's)	MM	Dingli_2006
Number of extranodal sites (NHL)	NHL	Lee_1999
Plasmablastic classification (MM)	MM	Rajkumar_2001
Comorbidity (HCT-CI) (1-3)	both	Sorror_2005
Affecting Mobilisation		
Age	healthy donors /Diffuse Large	Ings_2006 / Akhtar_2008 / Morris_2003

	Cell Lymphoma / MM	
Bone marrow involvement by tumour	MM / NHL	Demirer_1996, Perea_2001, Micallef_2000 / Kuittinen_2004
Previous radiotherapy	MM	Demirer_1996
Number of prior chemotherapy regimens	MM	Demirer_1996, Putkonen_2007
Duration from diagnosis to mobilisation	MM	Perea_2001, Popat_2009
Low baseline peripheral blood CD34+ count	both	Fruehauf_1995, Fruehauf_1999
Platelet count	NHL / Diffuse Large Cell Lymphoma / MM	Hosing_2009, Kuittinen_2004 / Akhtar_2008 / Putkonen_2007, Morris_2003
Previous treatment with alkylating agents	both	Lee_2003, Perea_2001
Prior fludarabine or lenalidomide treatment	both	Micallef_2000, Popat_2009
Weight	healthy donors	Ings_2006
Gender	NHL	Micallef_2000
Previous IFN use	MM	Putkonen_2007

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