

***EBMT***

***European Society for Blood and Marrow Transplantation***

# **MED-AB FORMS MANUAL**

***A Guide to the completion of the EBMT  
HSCT Med-AB Forms***



## INTRODUCTION

The present document contains information on how to fill in the MED-AB paper forms.

It is preceded by the definition of a haematopoietic stem cell transplant (HSCT) and information on when a new registration should be submitted to the EBMT. For general information on how to register data please visit <http://www.ebmt.org/registry/how-use-registry>

For downloads of the MED-AB forms please go to [www.ebmt.org/registry/data-collection](http://www.ebmt.org/registry/data-collection)

For information on submitting data directly to the EBMT database using ProMISe please refer to: [www.ebmt.org/registry/data-submission](http://www.ebmt.org/registry/data-submission)

Updated clinical manuals and reference documents are available to download from [www.ebmt.org/registry/data-submission](http://www.ebmt.org/registry/data-submission). We are grateful for any feedback as to its content (clarity of the definitions, omissions, insufficient background or excessive verbosity, etc.). Please send all comments to the EBMT Central Registry Office to the attention of Carmen Ruiz de Elvira at [carmen.ruiz@ebmt.org](mailto:carmen.ruiz@ebmt.org)

Many people have contributed to this manual, and we have a list of contributors at the end of this document. We would like to thank all those involved for their continuous support.

All hyperlinks in this document can be activated by pressing the Ctrl key and clicking on the link. This will take you to the correct page in the manual.

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EBMT Registry Head

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## TRANSPLANT DEFINITION

The EBMT has adopted the following definition for haematopoietic stem cell transplant (HSCT):

**TRANSFER OF STEM CELLS, DEFINED AS PROGENITOR CELLS WITH REPOPULATING CAPACITY AND THE POTENTIAL TO SUSTAIN LONG TERM HEMATOPOIESIS, WITHIN ONE PERSON OR FROM ONE PERSON TO ANOTHER, IN A DOSE THAT IS SUFFICIENT TO RESTITUTE HEMATOPOIESIS IN ALL LINEAGES.**

For an HSCT to be defined as such the aim must be to repopulate the bone marrow with the infused stem cells. There is no requirement for myeloablative therapy to be given for an HSCT to be defined as such.

## REGISTRATION OF NEW HSCT

A MED-AB Registration form should be filled in for a procedure in which a patient has received haematopoietic stem cells capable of long term survival or of self renewal. If the aim of the cell infusion is not a haematopoietic transplant or a donor lymphocyte infusion (DLI), please fill in the "Med-A for Cell Therapy (non HSCT)" form.

A centre must fill in a MED-AB Registration form only if the transplant procedure was actually performed at that centre.

The centre should **not** fill in the MED-AB Registration form if:

- they have acted only as a referral centre
- are only involved in following the patient after a transplantation procedure which has been performed elsewhere
- the harvest has been performed at this centre but the re-infusion has been performed elsewhere <sup>1</sup>

A new MED-AB Registration form should **not** be used if:

- the sole purpose of the procedure is to reduce a period of neutropenia after a chemotherapy treatment unlikely to cause troublesome neutropenia  
or
- the procedure is a donor lymphocyte or cytokine activated killer cells infusion; this should be entered as **Additional treatment** using the Med-AB Follow Up forms.  
or
- the procedure consists of the re-infusion of **Autologous** peripheral blood progenitor cells as a rescue for a failed graft. This may be called an auto 'boost' or 'top up'. This can be noted in **Additional treatment** using the Med-AB Day 100/Follow Up form.

### Is it an Allograft or a Boost?

An allo boost is an infusion of cells from the same donor without conditioning, with no evidence of graft rejection.

If cells are not from the same donor OR there is conditioning (chemo and/or TBI), OR there was evidence of graft rejection, then it is a genuine transplant.

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<sup>1</sup> An indication of this may be sent to the EBMT and can be acknowledged in the database once the transplant has been registered

**Tolerance induction in solid organ transplantation:**

HSCT may be performed in combination with a solid organ transplant e.g. kidney. A permanent partial engraftment (mixed chimerism) is the aim of this kind of stem cell transplantation in order to achieve immunological tolerance for the transplanted organ of the same donor and to eventually help acceptance of the organ. This is considered to be a stem cell transplantation rather than a cellular therapy. (Record the Main Indication Diagnosis as Uncoded (other) (code 88) and then in the Other Indication text field specify 'Tolerance induction in solid organ transplant')

**How many forms?**

For transplantation procedures in which there is only one instance of cell infusion, it is clear that only one MED-AB form will be filled. This is not so clear when the treatment of a single patient may consist of several instances of cell infusion. We list the most common situations:

Description of the procedure	Number of MED-AB's	Date of HSCT
Transplant with only one cell infusion	1	Date of infusion
Transplant with cell infusion distributed across several days	1	Date of 1 <sup>st</sup> infusion
Planned high dose sequential chemotherapy protocols with cell support*	<i>n</i>	Date of 1 <sup>st</sup> infusion after each high dose chemotherapy
Pre-planned double or triple transplant** each preceded by its own conditioning regimen	2 or 3	Date of 1 <sup>st</sup> infusion after each conditioning regimen
Autologous re-infusion after graft failure	none	

\* Planned high dose sequential chemotherapy protocols: Treatment by which the patient is subjected to *n* cell infusion episodes, separated by an interval usually less than 10 weeks, with each episode preceded by high dose chemotherapy. These entries should be marked as "Cell support = Yes" in the database, so that they can be readily identified.

\*\* Pre-planned double or triple transplant: Treatment by which the patient is subjected to 2 or 3 transplants. These transplants can be autologous or allogeneic or a combination. The sequence of transplants must have been decided prior to treatment and the interval between transplants can be as long as one year and are usually longer than 10 weeks.

## THE DATA COLLECTION FORMS

For detailed information on the data collection forms, please refer to [Submitting data to the EBMT](#)

No data items should be left blank unless specifically stated in the definition.

Patients who die after conditioning has started but before the transplant should also be reported. (ProMiSe users should register those patients entering the date of death as the date of HSCT. It is understood that this is not the date of HSCT since the transplant was never done. When you finish entering the planned transplant you will be asked for the Patient Status: please select code 3 - Died before HSCT but after Conditioning was initiated). For more info on Conditioning please see page 118

In the event of a case where the HSCT was aborted during or after Conditioning due to health reasons, and the patient is still Alive, you would still need to report all of the information. For more information, please see page 13 Type of HSCT

ProMiSe users: For orientation, the database field name has been added to the left of the item name in this document. If you opt to “show names” in the Actions menu in the Data Entry Editor, this field name appears on the right hand side of each item on the web page during data entry.

## TEAM

### **CENTNR** **EBMT Centre Identification Code (CIC)**

Every transplant centre on submitting data to the EBMT receives a CIC which should be entered here. If you do not know your CIC, look it up in the correspondence you have received from the EBMT Secretary or the Registry Office. If you still cannot find it, you can search for your centre in the EBMT website at:

<https://www2.clinicalresearch.nl/members/>

If you are yet not a member of the EBMT and want to report data, contact the EBMT at: [membership@ebmt.org](mailto:membership@ebmt.org)

This item is essential for proper registration of your data.

NOTE: If you are submitting several registrations in one go, you may want to omit the centre identification items that follow below in all registrations but the top one. However, this cannot be done if you have not entered your CIC code (see above).

### **UNIT** **Hospital**

Write the name in full of your hospital. Include the city and country.

### **Unit**

Write down the name of your Unit (i.e. Paediatric Haematology, Haematology, Oncology, BMT Unit, etc.). Entering this information is particularly important if your centre has more than one unit reporting independently to the EBMT. Ensure that you always use the same name in the future.

### **MEDNAME** **Contact person**

Write down the name of the person who will be responsible for updating or correcting the data contained within the MED-AB forms should this be necessary.

### **E-mail**

Write down the e-mail full address of the contact person, as defined above. If this person does not have a personal e-mail, write down the e-mail address of another person in the unit who would be willing to act as an intermediary.

**DAT1STRE** **Date of this report** (in First registration form). In database: Date of the 1<sup>st</sup> report  
 This is the date the Day 0 data for the first transplant of a single patient was collated or put together. If you enter the data directly from the patient notes, it is the date you are entering the data. If you fill in a Med-AB form, it is the date you filled in the form. This date will remain unchanged regardless of how much more data you add to the patient record.

**DATLSTRE** **Date of this report** (in Day 100 and Follow up forms). In database: Date of the last report  
 This is the date in which you collated or put together the last set of data you are about to enter. If you fill in a paper follow up form, for example, it would be the date you filled in the form.

**TRIAL** **STUDY / TRIAL**  
**Patient following national / international study / trial**  
 Indicate whether the patient has been included in a prospective study.

**STUDYNAM** **Name of study / trial**  
 If the answer to the above question is “Yes”, indicate here the official name of the study.

## PATIENT

**IDAA** **Unique Identification Code (UIC)**  
 The UIC is a combined number made of the CIC of the centre that performed the first HSCT or Cell therapy treatment in that patient, and a unique **Patient** number assigned to that patient by the database. If you submit paper forms, the National Registry assigns this **Patient** number when a new patient is registered into the database. If the patient has already been registered for a previous transplant or cell therapy treatment and you know their UIC number, then this should be entered on the form.

If you are entering a new patient in the EBMT database yourself, you can choose any free number suggested by the database, or enter a free number of your choice manually as **Patient** number. The **Patient** number forms part of the UIC, which is a unique database key, and should never be changed.

**IMPORTANT NOTE: ALL DATA FOR A PATIENT SHOULD BE ENTERED UNDER THE SAME UIC NUMBER**  
**This includes subsequent transplants.**  
**Patients transferred to other centres for further transplants must always keep their original UIC number.** If your patient had a prior transplant elsewhere please use the form [data access request form](#) found in the link below to request access to their existing UIC:  
[Patient Given Previous Treatment in Other Centre.pdf](#)

**UPN** **Hospital unique patient number or Code**  
 Write here the number/code used by the transplant centre to uniquely identify this patient. This is most likely to be the UPN (unique patient number) used by the hospital. **This item is compulsory.** It must be unique, by itself should suffice to identify the patient within the hospital environment and should not be liable to change. If a patient receives a second treatment, do not assign a new number: use the same unique number for this patient when registering subsequent HSCTs and/or cell infusions and register it in the same patient record.

**GIVNAME** **Initials (first name(s) surname(s))**  
 Write the initial of the first name of the patient followed by the initial of the surname of the patient. In countries where it is customary to do so, you can write down the initials of the first and second surname of the patient after the initial of the first name. If the local hospital guidelines or national law do not allow initials to be provided to third parties, you can write a code which has the approval of your hospital.

Make sure there is consistency in the way the identification of the patient is given so the record can always be traced even if the patient remains anonymous.

- DATPATBD** **Date of birth**  
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 to identify the registration when adding follow up data.
- PATSEX** **Sex**  
Indicate the gender of the patient at birth.
- ABOPAT** **ABO group and Rh factor**  
Indicate the blood group of the patient and the Rhesus factor status.

## DISEASE

- DAABB** **Date of diagnosis**  
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.  
  
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. (ProMISe users: contact the Registry Helpdesk for help on doing this.)
- DISMCLFD** **PRIMARY DISEASE DIAGNOSIS**  
Tick a box for the disease for which the patient is being treated.
- ACLEUK**  
Do not tick boxes for diseases the patient may have had in the past if the procedure being reported is not meant to deal with them. If the patient has a concurrent disease for which the transplant procedure can also be considered treatment (a concurrent autoimmune disease, for example), fill in the corresponding MED-AB forms.

## INITIAL DIAGNOSIS

Acute Leukaemia is a malignant disease that originates either in a lymphopoietic stem cell (Precursor lymphoid neoplasms, old ALL) or in a hemopoietic stem cell or progenitor cell (acute myelogenous leukaemia, AML). Either tumour is characterised by disordered differentiation and proliferation of these cells into lymphoblasts in precursor lymphoid neoplasms or myeloblasts in AML.

**VACLEUK DIAGNOSIS**

The EBMT has adopted the WHO (World Health Organisation) classification, as published in 2008.

**AML CLASSIFICATION OF DE NOVO AML AND RELATED PRECURSOR NEOPLASMS**

The WHO classification for AML and other haematological diseases, was proposed in the late 90's. It is in fact a classification based on the morphology of bone marrow cells, the presence of cytogenetic abnormalities (with or without molecular markers) and some clinical features. There were differences between the old FAB classification and the WHO classification, of which the most important difference concerns the number of blasts used to arrive at a diagnosis of AML which was reduced from 30 to 20%. Moreover, new categories were added with the presence of cytogenetic abnormalities and molecular markers (if present). Some of the new categories are in agreement with FAB classification, for example in the "not otherwise specified", Acute erythroid leukaemia is FAB M6.

Worth noting is the diagnosis of "AML with myelodysplasia related changes". In most cases, this classification applies to AML where an MDS or an MDS/MPN **has been diagnosed** beforehand. In a few cases, it applies to what looks as a *de novo* AML at the time of diagnosis, but which after further analysis of the bone marrow or after treatment for the AML, there is a suggestion that there could have been an undetected history of myelodysplastic syndrome (MDS).

**Previous diagnosis of MDS**

In cases where the "AML with myelodysplasia related changes" classification applies, a further question needs to be answered regarding whether MDS had or had not been previously diagnosed. If MDS or MDS/MPN was diagnosed and then transformed to AML prior to HSCT, answer "yes" to **Previous diagnosis of MDS**; complete the MDS form until **Status at HSCT**, and then return to the Acute Leukaemia form.

The WHO classification also includes the "Therapy related neoplasms" (old "Secondary Acute Leukaemia") which are considered the consequence of previous treatment for other malignancies.

**ALL CLASSIFICATION OF PRECURSOR LYMPHOID NEOPLASMS**

As for the AML, a WHO classification is used for precursor lymphoid neoplasms. It is a classification based on the immunological aspects of bone marrow cells and the presence of cytogenetic abnormalities (with or without molecular markers) and some clinical features. FAB classification of precursor lymphoid neoplasms is not used.

Sometimes there are difficulties in the diagnosis of lymphoblastic lymphoma: this is a variant of precursor lymphoid neoplasm, defined as manifestations of phenotype and genotype without BM infiltration. If in doubt, contact the Registry with more details.

**VACLEUK CLASSIFICATION OF OTHER ACUTE LEUKAEMIAS****Mixed Phenotype Acute Leukaemia**

Double fluorescence techniques have permitted the identification of at least three types of leukaemia cell heterogeneity: mixed or bilineage with two distinct populations of blast cells (myeloid and lymphoid, or T and B lymphoid), a single population of blast cells with markers for both myeloid and lymphoid lineage (biphenotypic expression) and a transformation from one cell line to another after treatment. In case of doubt regarding the

**VDIAGTX** classification ask your physician.

**VPREDISP Predisposing Condition prior to Leukaemia diagnosis**

AML may develop under certain predisposing conditions such as the hereditary diseases Fanconi, Bloom, Down Syndrome. Please indicate whether a genetic non malignant condition could have predisposed the patient to develop AML. If the patient did not have this type of condition and the AML developed after a prior malignancy (therapy related or MDS type changes), you should answer “no” to this question.

**RPDRGRAD Donor Cell Leukaemia**

AML may also develop in donor cells when the patient has had a previous allograft. Please, indicate if this is the case for a patient that fulfils this condition.

**VCHROMOS CYTOGENETICS**

Chromosomal alterations have been demonstrated in bone marrow cells from a majority of patients with acute leukaemia and their characterizations have many prognostic implications. Sometimes, mainly in precursor lymphoid neoplasms, the chromosome analysis can fail and this should be indicated. However, with the new techniques of DNA analysis, molecular alterations can be detected. To complete this item you should confer with the cytogenetics laboratory or your physician. If it is not possible, please send a copy of the results.

The cytogenetic abnormalities can be characterised as changes involving chromosome number (ploidy) or chromosome structure (translocation, inversion).

Generally the definition of **complex karyotype** involves 3 or more abnormalities. A **monosomal karyotype** is defined by 2 or more autosomal monosomies or 1 autosomal monosomy and at least one other structural abnormality.

**VNUMETAN Number of metaphases with anomalies / number of metaphases examined:**

**VMETAPEX** this gives important information on the percentage of metaphases with anomalies and is always given in the results of the cytogenetic analysis. It is essential information to know the accuracy of the measurement

**Example of a typical cytogenetic result or karyotype:**

Results: 47, XX, + 11 [25] / 46, XX [8]" The number within [ ] represents the number of metaphases analysed. This is 25 for the metaphases with 47, XX,+11 and 8 for the metaphases with 46, XX. XX is female, but a female has 46 chromosomes and this female has 25 metaphases with 47 chromosomes. This is due to an additional chromosome number 11, given as +11 (trisomy 11), making the total of chromosomes in each of the 25 metaphases analysed 47. The patient has also 8 metaphases with 46, XX and this is normal for a female. The total of metaphases analysed is 25 plus 8 = 33.

It is very important to describe each abnormality by their presence or absence, since we can observe more than one abnormality and if you tick only the presence, at the moment of the analysis we will not be sure if the others abnormalities were searched or not.

**MOLEBIO MOLECULAR BIOLOGY**

The molecular biology methods are varied. The one best known is the PCR (Polymerase Chain Reaction). Molecular biology can detect gene markers for specific leukaemias. Most common gene markers are the presence of bcr-abl in Philadelphia positive chromosome precursor lymphoid neoplasms and pml-rar in AML M3. If markers are present, indicate clearly which have been found. It is important to identify each marker separately, indicating whether they have been evaluated or not.

If molecular biology analyses are done and no markers are found, please tick Absent.

**NOTE ON CYTOGENETIC ABNORMALITIES & MOLECULAR MARKERS**

You can have a diagnosis with specific abnormalities that still presents a normal cytogenetic analysis. Cytogenetics (both conventional karyotyping and FISH analysis) captures gross chromosomal alterations (losses and gains of chromosome regions, chromosomal translocation,...) while molecular analysis is able to detect a unique nucleotide/DNA base substitution (point mutation) or small insertion/deletions (in/dels) in determinate genes within a normal karyotype. For example, an AML with NPM1 mutation or with CEBPA double mutation can be found in

patients presenting normal cytogenetics.

In another example, most recurrent AML translocations/rearrangements can be identified by both cytogenetic and molecular analysis (RT-PCR of the corresponding fusion gene). In exceptional cases, a chromosomal translocation can be cytogenetically "cryptic" i.e., with an apparent normal karyotype, but with the involved gene fusion: this may be the case with an AML with RUNX1-RUNXT1 rearrangement/gene fusion, but without detectable typical chromosomal translocation t(8;21)(q22;q22).

**NB:** it can happen that in clinical notes some abnormalities are called "Wild type". For example, if you see "NPM1 wild type" it means that the NPM1 abnormality is Absent (wild type means No mutation).

#### WBCD

#### White Blood Cells (WBC) Count at diagnosis

Please, pay attention at the units for number of WBC at diagnosis:  $10^9/L$  is the same as  $10^6/ml$  or  $10^3/\mu l$ . If the WBC is given in  $mm^3$  than you should fill in as  $10^9/L$ :  $300.000mm^3$  is the same as  $300 \times 10^9/L$ . If the measurement is unavailable, please tick the box "Not available".

#### IDAABECK

#### INVOLVEMENT AT DIAGNOSIS

#### ORGANOTS

In acute leukaemia the bone marrow is almost always involved, but other organs may also be affected by the leukaemia. Mark all sites applicable.

Granulocytic Sarcoma is an extramedullary aggregate of blast cells (composed of immature granulocytic cells). This disease occurs most commonly in patients with acute leukaemia of the myeloid type. Sites most often affected are bone (especially the skull, spine, ribs, long tubular bones, and sternum). They also involve a variety of soft tissues: periosteum, soft tissue, orbit, lymph nodes and skin.

## FIRST LINE THERAPY

#### VPRETRAT

#### FIRST THERAPY GIVEN

Indicate whether the patient has been treated before the transplant procedure. This will be the case for practically all patients. If the diagnosis is AML skip this question and go to date of HSCT. However if it is precursor lymphoid neoplasm you should complete.

Drugs that block the Tyrosine kinase receptors have been successfully used in patients with CML but also precursor lymphoid neoplasms with t(9;22) or bcr-abl, therefore results of chemotherapy have been very encouraging. However the impact of the use of those drugs previous to HSCT is unknown. Collecting this data we will be able to analyse the result of HSCT in patients in which these drugs are being used.

## DATE OF HSCT

#### IDAABC

#### DATE OF TRANSPLANT

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.

## DISEASE HISTORY BEFORE 1<sup>st</sup> TRANSPLANT *(see below)*

This section is applied only for first transplants

One of the most important factors affecting outcome after transplant is the history of the disease before transplant. All dates of complete remissions and relapses (on or off therapy) are of major importance. You should verify the accuracy of the data reported in the different items of this section. For example, sometimes a patient reported as having had a first relapse are then reported to be transplanted in first complete remission (CR), which is clearly impossible.

Remissions, within the pre-transplant treatment section, are always defined as **haematological remissions** (see definition below). **Cytogenetic** and **molecular remissions** are more difficult to define, since it depends on the techniques used to quantify the chromosome abnormalities. In case of doubt, ask your physician and specify which definition has been used.

#### **VPRETRAT FIRST THERAPY GIVEN**

Indicate whether the patient has been treated before the transplant procedure. This will be the case for practically all patients.

#### **VCRPRETR FIRST REMISSION SINCE DIAGNOSIS AND BEFORE 1<sup>ST</sup> HSCT**

Read this question as first complete remission. The concept of partial remission (PR) is not applicable to acute leukaemia.

**IDAABE** Complete remission (CR) is defined as meeting all of the following response criteria for at least four weeks:  
**VDISESTA**

- < 5% blasts in the bone marrow
- No blasts with Auer rods (*applies to AML only*)
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Transfusion independent

If the bone marrow is aplastic, even in the absence of blasts, it cannot be considered a CR but should be reported as "Hypoplasia without blasts".

**ETC...**

If there was a CR, fill in the date of CR. Usually there is an indication of the month at which a CR has been achieved in the pretransplant letter or letter from the referring centre. A complete haematological remission is assessed with a bone marrow puncture and with a lumbar puncture if patient had CNS localisation. Therefore, look for a date at which a bone marrow puncture was performed and for which the conclusion is "complete remission". If patient had CNS localisation, the cerebro-spinal fluid has to be free of leukaemia cells.

Indicate the number of courses it took to obtain the first CR as Number of induction courses.

#### **FIRST RELAPSE SINCE DIAGNOSIS AND BEFORE 1<sup>ST</sup> HSCT**

The pre-transplantation letter gives a summary of the patient's medical treatment/history since diagnosis. In the event that a relapse occurred, it is mentioned in the pretransplant letter along with the site of relapse.

**V1STRELA** A relapse can only occur if a complete remission had been achieved.

Relapse is defined as the apparition of more than 5% blasts in the bone marrow or presence of extramedullary disease after a period of complete remission.

**IDAABE** If there is a relapse, an indication of the month at which the relapse occurred is given in the  
**VDISESTA** pretransplant letter. Search for the precise date in the patient's file. A complete haematological  
**ETC** remission is assessed with a bone marrow puncture. Therefore, look for a date at which a bone marrow puncture was performed and for which the conclusion is "relapse" or for which the "blasts" percentage is above 5%.

**IDAABECK** Site of relapse  
**ORGANOTS** Tick all sites affected. See definition of Granulocytic Sarcoma above.

## VTRANTYP TYPE OF HSCT

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic            the patient receives stem cells from another person  
Autologous        the patient receives his/her own stem cells back

Other                in extremely rare cases the graft may not fit into either category above. If you have a complex auto/allo case please contact [Registry Helpdesk](#) first with more details, and they will advise you on how to proceed with your registration. An example of such would be a case where the HSCT was aborted *during* or *after* Conditioning due to health reasons, and the patient is still Alive, when you would still need to report all of the information. Please enter the planned transplant as usual, and indicate whether it was Auto or Allo. (Moreover, if you enter MedB form, please add "0" to the Cells Infused question) At the end of the form, at Survival Status, please select code 9. Lost to Follow Up. The Registry Helpdesk will specially "mark" the patient record as Type of HSCT = Complex, requires explanation.

## STATUS OF TREATMENT AND DISEASE AT STEM CELL COLLECTION

*AUTOGRAFTS ONLY; CONCERNS ONLY MATERIAL ACTUALLY REINFUSED*

The status of the disease should always refer to the date on which the cells actually re-infused where collected (or "harvested"). For example: sometimes patients undergo more than one instance of stem cell collection. Stem cells may be collected (collection I) but not infused because the patient relapsed after this collection before the transplantation could be performed. This patient can then be treated with a second remission-induction and consolidation course in order to attain CR. In this case, this patient will most probably not be transplanted with the stem cells that were collected earlier (collection I) before the patient relapsed because it is likely these stem cells were contaminated with leukaemia cells. In this case, during the second consolidation course an attempt can be made to collect stem cells for the second time (collection II) and transplantation may be done with these stem cells. In this case it is the state of the disease at this second time (collection II) that should be entered here.

VNUMSTM Write if the patient was transplanted in First, Second or Third CR, or in First, Second or Third relapse, or at a refractory stage (no response to treatment). If you have any doubt, do not hesitate to ask your physician. This is a very important item.

## VDISESTA DISEASE

**Primary induction failure** means the patient despite treatment has never achieved first complete remission.

**Complete remission (CR)** is defined as no blast cells in the peripheral blood and no more than 5% blasts in the bone marrow. CR requires that bone marrow biopsy has been done, otherwise it cannot be evaluated. This definition is related to the haematological remission if type of remission is not specified.

The above must be accompanied by sufficient cellularity and signs of regeneration of normal cellularity. If the bone marrow is aplastic, even in the absence of blasts (hypoplasia without blasts), it cannot be considered a CR but should be reported as "Other".

*FOR COMPLETE REMISSION ONLY:*

In order to follow the evolution of the abnormalities detected at diagnosis, we would like to know if they still persist at the time of stem cell collection or not.

## VCYTOGRE Cytogenetic / Molecular Remission

VMOLECRE To be completed only if patient in complete remission

### Type of Remission

If a chromosomal abnormality or a specific molecular marker had been detected at diagnosis, please specify whether they are absent at this time point, or whether they still persist

If abnormalities were not tested at this time point, please tick "Not Evaluated"

If abnormalities have never been detected before the time point, please tick “Not applicable”

**Relapse** is defined as the apparition of more than 5% blasts in the bone marrow after a period of complete remission.

Progression is not a relevant term in acute leukaemia

## STATUS OF DISEASE AT TRANSPLANTATION

**VDISESTA** The disease status just before conditioning should be assessed and reported here. This is true even if the patient's disease status was assessed at mobilisation or collection in the autograft setting. The disease at stem cell collection and at transplantation may not be the same since the disease may have changed in the interval.

See above, under “Status of treatment and disease at stem cell collection” for definitions.

## RESPONSE OF DISEASE

**TUMRSA2** At approximately 100 days after transplant you should fill in the status of the disease. Definitions as above.

### Med-A only

#### Current disease status

You must tick only one box. Indicate if the patient is in complete remission or not.

For baseline refer to “STATUS AT TRANSPLANT.

*The response date is the date that the sample or image was taken for assessing the response*

#### Date achieved

If the patient is in CR, enter the date it was achieved or assessed.

#### Date assessed

If the patient is not in CR enter the last date the patient's disease status was assessed.

## FOLLOW UP

## ACUTE LEUKAEMIA

**VRELPROG** **RELAPSE OR PROGRESSION AFTER TRANSPLANT**

☐ Previously reported

☐ Yes, date of relapse/progression      ..... - ..... - .....  
dd                      mm                      yyyy

**VRELLEUK** **Haematological relapse** is defined as any increase of blast cell count over 5% in the bone marrow or presence of extramedullary disease. Indicate the 1<sup>st</sup> date it was noted.

**VRELLEU3** **Cytogenetic relapse** is defined as reappearance of chromosome anomalies detected earlier in the history of the disease. Cytogenetic relapse can only be determined if cytogenetic remission has been previously demonstrated. You should discuss the definition of cytogenetic relapse with the responsible medical doctor. Indicate the 1<sup>st</sup> date it was noted; this may be different from the date of haematological relapse.

**VRELLEUS** **Molecular relapse** is defined as reappearance of acute leukaemia specific molecular markers detected earlier in the history of the disease. Molecular relapse can only be determined if molecular remission has been previously demonstrated. You should discuss the definition of molecular relapse with the responsible medical doctor. Indicate the 1<sup>st</sup> date it was noted; this may be different from the date of haematological or cytogenetic relapse.

All other items asked in the follow-up have been defined above or in the General follow up chapter of this manual.

SPECIFICATIONS  
OF THE DISEASE**BONE MARROW FAILURE SYNDROME**  
(INCLUDING APLASTIC ANAEMIA)

## INITIAL DIAGNOSIS

Bone marrow failure syndromes are disorders of the hematopoietic stem cells that can involve one or several cell lines. They can be acquired (*non constitutional*) or genetic (*constitutional*).

**SUBCLASSIFICATION****Acquired**

These are non constitutional syndromes (the aetiology cannot be congenital or genetic)

☐ **Aplastic anaemia**

Aplastic anaemia (AA) is a bone marrow failure syndrome characterised by bicytopenia (decrease in two of three cell lines) or pancytopenia (decrease in all blood cell lines) in the peripheral blood and an aplastic (absence of cellular proliferation) or hypoplastic/hypocellular (insufficient cell proliferation) bone marrow in the absence of major dysplastic features or neoplastic (=malignant) cells and in the absence of chemotherapy- or radiation therapy induced damage, or increased reticulin. At least two out of the following three criteria have to be fulfilled:

- neutrophils  $< 1.5 \times 10^9/L$
- platelets  $< 50 \times 10^9/L$
- reticulocytes  $< 60 \times 10^9/L^*$

Aplastic anaemia is classified as very severe (vSAA), severe (SAA) and non severe aplastic anaemia (nSAA) on the basis of peripheral blood counts. Therefore it is important to get the information on blood counts at first immunosuppressive treatment episode.

Criteria for vSAA, SAA and nSAA are as follows:

**nSAA:** 2 out of 3 criteria

neutrophils	$< 1.5 \times 10^9/L$
platelets	$< 50 \times 10^9/L$
reticulocytes	$< 60 \times 10^9/L^*$

**SAA:** 2 out of 3 criteria

neutrophils	$< 0.5 \times 10^9/L$
platelets	$< 20 \times 10^9/L$
reticulocytes	$< 20 \times 10^9/L^*$

**vSAA:**  
same criteria as SAA, but neutrophils  $< 0.2 \times 10^9/L$  (obligatory)

\* using an automated analyser

☐ **Pure red cell aplasia (*non constitutional* PRCA)**

**Pure red cell aplasia (PRCA)** = isolated impairment of erythropoiesis (generation of red blood cells), i.e. these patients suffer from anaemia only. In contrast to patients with aplastic anaemia, leukocyte and platelet count is normal in PRCA patients. There is absolute reticulocytopenia (reduction of the absolute number of reticulocytes below the lower limit of the normal range). The marrow is normocellular and there is a marked erythroid hypoplasia (lack or paucity of recognizable erythropoietic cells in the bone marrow).

If PRCA is of genetic origin, it is called Diamond-Blackfan Anaemia (DBA) ( see below).

☐ **Paroxysmal nocturnal haemoglobinuria (PNH)**

**Paroxysmal nocturnal haemoglobinuria (PNH)** = acquired disorder of hemopoietic stem cells. PNH is always acquired. Its clinical course is characterised by hemolysis (chronic or acute) and/or thrombosis. Often it is associated with aplastic anaemia (might precede aplastic anaemia or might

occur as a late clonal complication after aplastic anaemia). Combination of symptoms (hemolysis, thrombosis, bone marrow failure) and severity may vary greatly.

Please fill which of the symptoms PNH is associated with at diagnosis (you can tick more than one box):

Haemolytic  
Aplastic  
Thrombotic  
Other: .....

If criteria for both aplastic anaemia and PNH is fulfilled, tick "Aplastic anaemia" and enter details on PNH later on when asked.

☐ Pure white cell aplasia

**Pure white cell aplasia (PWCA)** = isolated impairment of the white cell lineages. It may be associated with thymoma and/or hypogammaglobulinemia.

If PWCA is of genetic origin, it is called Shwachman-Diamond (see below).

☐ Amegakaryocytic thrombocytopenia (*non constitutional*)

**Amegakaryocytic thrombocytopenia** = can be as:

- thrombocytopenia due to reduction or absence of megakaryocytes (precursor cells of platelets) in the marrow.
  - otherwise, normocellular bone marrow with normal erythropoiesis and granulopoiesis.
- It can also be genetic.

☐ Other: .....

If the acquired syndrome is not listed above, write it in plain text. Use the WHO official name for the diagnosis.

**ETIOLOGY** (= cause of the disease)

- ☐ Idiopathic  
☐ Post-hepatitis  
☐ Toxic (*includes drug induced*)  
☐ Other, specify.....

idiopathic	no recognisable cause; in the majority of patients disease is classified as "idiopathic" (since there is no evidence for any other etiology like post-hepatitis, drug-induced etc)
Post-hepatitis	documented infection with a hepatitis virus preceding the onset of BMF. The virus inducing this hepatitis-aplastic anaemia syndrome has still not been identified.
Toxic	some drugs can induce BMF (e.g. gold salts, penicillamine, phenylbutazone; ibuprofen, indomethacin; antiepileptics: hydantoins, carbamazepine; chloroquine, phenothiazines, antithyroid drugs, allopurinol, sulphonamides); also toxic elements (i.e. benzene) can induce aplastic anaemia.
Other	This can include infections with other virus: Epstein-Barr-Virus infections and other herpes virus infections and influenza A infections can, in some rare cases, be complicated by aplastic anaemia

**Genetic**

Although still very rare, Fanconi is the most frequent of the genetic bone marrow failures.

☐ Fanconi

**Fanconi** = congenital aplastic anaemia characterised by progressive bone marrow failure, an increased risk of developing cancers (acute leukaemia and other malignancies); typical birth defects (skin pigmentation, short stature, hypoplasia of thumb and radius, microcephaly, microphthalmia, urinary tract defects, cardiac anomalies).

In vitro diagnostic tests:

-sensitivity to chromosomal breakage by DNA cross-linking agents (= positive "chromosomal breakage test")

-molecular basis: mutations in at least eight distinct genes ("Fanconi anaemia genes" FANCA, B, C, D1, D2, E, F, G, FANCA, FANCC etc.)

Fanconi anaemia is characterised by bi-lineage or tri-lineage cytopenia and hypoplasia or aplasia in the bone marrow. It is genetically heterogeneous and the different genetic sybtypes are known as "Fanconi complementation groups".

There are 12 known complementation groups that cause Fanconi Anemia when they undergo pathogenic mutations. The groups are A, B, C, D1, D2, E, F, G, I, J, L, and M. The genes that correspond to these groups are given names like FANCA (the most common cause of FA), FANCB, FANCC, FANCD1 (recently discovered to be the BRCA2 gene!), FANCD2, FANCE, FANCF, FANCG, FANCI, FANCI (also BRIP1), FANCL (also PHF9 and POG), and FANCM (also FAAP250). So 11 of at least 12 Fanconi Anemia genes have now been identified--the only one outstanding to be identified is FANCI.

Other genetic bone marrow failures include:

☐ Diamond-Blackfan (*congenital / constitutional PRCA*)

See PRCA under Acquired, above.

☐ Shwachman-Diamond Syndrome

**Shwachman-Diamond Syndrome** = a rare genetic disorder that affects many organs in the body, which symptoms could vary from individual to individual. The primary features include: bone marrow problems (leading to inadequate production of some types of white blood cells e.g. neutropenia, pancytopenia with aplastic anaemia or myelodysplastic syndrome), an exocrine defect in the pancreas (leading to malabsorption), skeletal abnormalities such as metaphyseal dysostosis, and short stature.

☐ Dyserythropoietic Anaemia

**Dyserythropoietic anaemia** = a group of autosomal recessive anaemias characterised by ineffective erythropoiesis, bone marrow erythroblastic multinuclearity, and secondary haemochromatosis.

☐ Dyskeratosis congenita

**Dyskeratosis congenita (DKC)** = (or Zinsser-Cole-Engman syndrome) a rare progressive congenital disorder ; it is characterized by a triade of symptoms: (1) cutaneous hyper-pigmentation , (2) nail dystrophy and (3) leukoplakia of the oral mucosa. Other symptoms may include cirrhosis, lung fibrosis, osteoporosis, avascular necrosis of bone, continuous lacrimation, anaemia, testicular atrophy. DKC is the typical disease of short telomeres, and is caused by a mutation in DKC1 (X-linked recessive), TERT, TERC or TINF2 genes (autosomal dominant) among other genes. In vitro diagnostic tests are: telomere length analysis (by flow cytometry or PCR) and TERT/ TERC mutation studies.

☐ Amegakaryocytic thrombocytopaenia  
(*constitutional*)

See Amegakaryocytic thrombocytopenia (*non constitutional*) under Acquired, above.

☐ Other: .....

If the genetic syndrome is not listed above, write it in plain text. Use the WHO official name for the diagnosis.

## CYTOGENETICS

### Chromosome analysis

☐ Normal

☐ Abnormal

☐ Not done or failed

☐ Unknown

VCHROMOS

VABNORMA

Cytogenetics is the technique by which chromosomal abnormalities are detected. Most of the patients with BMF have normal karyotypes in the cytogenetic analysis. In a substantial proportion of patients interpretation is not

VFAMSNDX

possible because of low number of cells to examine due to bone marrow aplasia (tick "fail"). In some patients, however, chromosomal abnormalities do occur and can be detected in a subpopulation of cells. Please indicate

VCHRXNRD

whether the listed abnormalities are absent or present. If other abnormalities have been found indicate the type and chromosomes involved under Other or associated abnormalities

The standard blood test to diagnose Fanconi Anemia is the **Chromosomal breakage test**. The chromosomes are put under stress and if they exhibit chromosome breakage, the test is considered positive for Fanconi anemia.

### HAEMATOLOGICAL VALUES

Fill in the blood count values before start of the first immunosuppressive treatment episode, i.e. before immunosuppression or stem cell transplantation if patient goes straight to transplant.

<b>HBP</b>	Hb (g/dL)
<b>PLATP</b>	Platelets ( $10^9/l$ )
<b>VNEUTRTR</b>	Neutrophils ( $10^9/l$ )
<b>RETICP</b>	Reticulocytes ( $10^9/L$ )
<b>FERRITI</b>	Ferritin (ng/ml)

Important: fill in the **absolute count** of neutrophils ( /  $10^9/L$ ) (**please no (!) percentages**)

fill in the **absolute count** of reticulocytes ( /  $10^9/L$ ) (**please no (!) percentages**)

These values are very important for:

- (i) classification of BMF
- (ii) evaluation of prognostic parameters
- (iii) evaluation of response to treatment (since classification of response depends on initial blood count prior to definitive treatment; see below)

<b>VTRANS1</b>	<b>Hb</b>	Tick "Transfused" if patient received RBC transfusion within 4 weeks before blood count was taken
<b>VTRANS2</b>	<b>Platelets</b>	Tick "Transfused" if patient received platelet transfusion within 1 week before blood count was taken

Haemorrhages / Resistance to random platelets / Systemic infection

Check the boxes if the patient has one or more of these complications before first immunosuppressive treatment episode; if none, please, remember to tick "no" in each box.

<b>VHEMORR1</b>	<b>Haemorrhages:</b> Many patients with BMF seek medical attention because of bleeding (easy bruising; red spots ("petechiae"), bleeding gums, nosebleeds ("epistaxis").
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<b>VRRP1RX</b>	<b>Resistance to random platelets:</b> An increment less than $10 \times 10^9/L$ on at least 2 occasions of ABO-identical platelet transfusions (in the absence of non-immune factors causing inadequate increment of platelets after transfusion: fever, systemic infection, treatment with amphotericin, disseminated intravascular coagulation, splenomegaly).
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<b>INFNRP</b>	<b>Systemic Infection:</b> Defined as: infection is presumed if there is proof of a primary microbiological pathogen and/or if there are typical clinical signs or symptoms or laboratory evaluations and/or if there is fever not likely to be due to non-infectious cause such as drug or blood product administration etc. (Fever is defined as body temperature $> 38.0^\circ C$ on two or more occasions within 12 hours or $\geq 38.5^\circ C$ on one occasion).
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<b>VPNHTEST</b>	<b>PNH TESTS</b> A substantial proportion of AA patients carry a population of cells with a "PNH phenotype", i.e. cells which are missing the expression of a specific class of surface proteins ("GPI-anchored proteins" ) due to an acquired mutation in the PIG-A gene.
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<b>VGPIANCD</b>	Presence of PNH is typically tested by <b>Flow cytometry</b> of the expression of GPI-anchored proteins (e.g. CD55, CD58, CD59, CD14, CD16, CD66b, etc.). Indicate the size of the PNH clone and the type of cells
-----------------	--

used for the assessment. This information is usually found among the haematology laboratory results, but possibly in a page different from the full blood count results but with the flow cytometry results.

**VPNHTESO** **Other:** please, specify the type of the test and the result if different from flow cytometry.

**VDATPNHT** Tick the appropriate boxes to indicate positive or negative results of these tests and write the date the test(s) was performed; if tests are not done, please tick the appropriate box. Do not leave blank.

Clinical manifestations of PNH ☐ No ☐ Yes

These include cytopenias, thrombocytopenia, neutropenia or anaemia, thrombotic complications such as the Budd Chiari syndrome (hepatic vein thrombosis) or thromboses in different locations and active haemolysis which may manifest by dark urine, flank pain, elevated LDH. PNH patients may also exhibit cramps of bowel, esophagus, erectile dysfunction, or other muscles.

## FIRST IMMUNOSUPPRESSIVE TREATMENT EPISODE

DEFINED AS ANY TREATMENT COMBINATION CONTAINING ONE OF THE FOLLOWING COMPONENTS: STEM CELL TRANSPLANTATION, ANTITHYMOCYTE or ANTILYMPHOCYTE GLOBULIN, CYCLOSPORINE A, MYCOPHENOLATE MOFETIL, or HIGH-DOSE CYCLOPHOSPHAMIDE

The pages on therapies refer to immunosuppression to be filled in for patients who either received immunosuppression only or immunosuppression regimen(s) before subsequent HSCT.

**VPRETRAT** Patients can be initially treated with androgens, steroids, cytokines or other agents. Many patients receive this type of treatment (in particular very often steroids) before being referred to a specialized treatment centre. However, this is not considered "definitive treatment" since the efficacy of this type of treatment for aplastic anaemia is very low (androgens) or absent (steroids).

The FIRST IMMUNOSUPPRESSIVE TREATMENT EPISODE refers to the following types of treatments, which can induce at least partial response, or even cure of the disease:

- antithymocyte globulin (ATG) or antilymphocyte globulin (ALG)
- cyclosporine A (CsA) or tacrolimus
- mycophenolate mofetil
- monoclonal antibodies
- (high dose) cyclophosphamide

### WAS THE PATIENT TREATED BEFORE THE HSCT PROCEDURE?

If the patient goes straight to HSCT, answer NO. In this case the first treatment episode is the HSCT itself.

If the patient has received treatment before the HSCT, or the form is being used for the registration of Immunosuppressive therapy only, enter the first date of the treatment for that particular episode.

**VSEQNUMB** The sequential number of the treatment episode must be counted from the very first immunosuppressive treatment episode for the patient, which may have been already registered.

If first treatment ever:

#### NUMBER OF TRANSFUSIONS BEFORE THE 1ST TREATMENT

**VRBCTRAN**  
**VNBPLATT** Count the total number of units of RBC or platelets transfused between first occurrence of cytopenia and start of first immunosuppressive treatment episode and tick appropriate boxes.

If subsequent treatment:

Enter haematological values before the treatment and the reason for this subsequent treatment. The haematological values must have been collected within the 3 months prior to the treatment.

**VREASL2**

#### REASON FOR THIS TREATMENT

Patients often receive more than one course of immunosuppression. Sometimes patients have complex treatment history. It is very important to know the reason for *each* repeated cycles.

- It might be failure of previous cycles (=No response), partial response (PR) after previous cycle, relapse (which is common, > 40% of responders relapse) or –rarely- secondary clonal disorder. See definitions below.

**VCHEMOT**

☐ ATG, etc.

The list contains the main drugs for immunosuppression and supportive therapy used for bone marrow failures. Choose one or more of these options presented and record start date and end date for each drug.

Make sure you fill in the immunosuppression separately from the conditioning regimen even if the same drugs are mentioned for both treatments (e.g. ATG or cyclophosphamide may be used both for immunosuppression and conditioning).

Choose one or more of these options presented and record start date and end date for each drug. Supportive drugs are given along with immunosuppression treatment in order to ameliorate side effects of treatment: e.g. steroids which prevent or aid in the relief of serum sickness (an adverse event of ATG treatment) or to improve symptoms (e.g. G-CSF to increase neutrophils to prevent infection).

For ATG only, indicate the animal origin of the immunoglobulin, together with the brand and dose in mg/kg.

**TUMRSA2****RESPONSE TO THIS IMMUNOSUPPRESSIVE TREATMENT EPISODE****DATRESP**

Report best response achieved after first key therapy and date of response evaluation.

For Aplastic anaemia it is essential to check the parameters measured with those at the onset of treatment (diagnosis for the 1<sup>st</sup> treatment; status at the onset of each treatment, for any subsequent treatment), since the definitions of response are dependent on the type of AA before treatment: nSAA, SAA or vSAA. For example, if a patients with SAA relapses after the 1st immunosuppression treatment to non severe aplastic anaemia (nSAA), the baseline for response evaluation of the 2nd treatment episode is the status before the second treatment (in this case nSAA) and not the status before 1st treatment.

Definition of response:

for **Severe Aplastic Anaemia (SAA and vSAA):**

- Complete response:** haemoglobin normal for age  
neutrophils  $\geq 1.5 \times 10^9/L$   
platelets  $\geq 150 \times 10^9/L$
- Partial response:** transfusion independent  
no longer meeting criteria for severe aplastic anaemia (see above)
- Poor partial response:** transfusion independent  
levels of hemoglobin, neutrophils and platelets still meeting criteria for severe aplastic anaemia (see above)
- No response:** still meeting criteria of severe aplastic anaemia and transfusion dependence

for **Non-Severe Aplastic Anaemia (nSAA):**

- Complete response** same criteria as for severe AA
- Partial response** transfusion independence (if previously required)  
or doubling or normalization of at least one cell line  
or increase above baseline\* by  
3 g/dL hemoglobin and  
0.5x10<sup>9</sup>/L neutrophils and  
20x10<sup>9</sup>/L platelets.

**No response**

not meeting criteria of partial or complete response

For **Fanconi**, the criteria is similar to AA. Unfortunately, for other Bone Marrow failure syndromes there is no established uniform criteria. However, the response definitions for nSAA can be adapted for unilineage or bilineage BMF.

**SECONDARY CLONAL COMPLICATIONS**

Answer **Yes** if the patient has developed myelodysplastic syndrome (MDS), acute leukaemia, or paroxysmal nocturnal haemoglobinuria (PNH). See section on PNH, above, for details on assessment of this complication.

## ADDITIONAL IMMUNOSUPPRESSIVE TREATMENT EPISODE

Same definitions as in the section “First immunosuppressive treatment episode” apply.

If more than one additional episode, copy this section of the Med-B Form and submit as many times as necessary.

## STATUS AT HSCT

All clinical measurements are to be done before *start of conditioning* for stem cell transplantation. See previous sections for definitions.

**NUMBER OF TRANSFUSIONS FROM DIAGNOSIS**

VRBCTAN

Count the total number of units of RBC or platelets transfused from diagnosis to start of conditioning, including those already reported just before the first immunosuppressive treatment.

VNBPLATT

Tick appropriate boxes to indicate whether the product had been irradiated prior to transfusion .

## ADDITIONAL TREATMENT POST-HSCT

**ADDITIONAL DISEASE TREATMENT**

- ☐ No
- ☐ Yes: ☐ Planned (*planned before HSCT took place*)
- ☐ Not planned (*for relapse/progression or persistent disease*)

Please specify whether or not additional treatment was given. You are also asked to specify whether this treatment had been planned as part of the original transplant protocol (Planned) or whether it is a reaction to an event (or lack of an expected event, ie: obtaining a CR) that has taken place in between the transplant and this follow up (Not planned). Note, however, that it is rare to have planned treatment after HSCT for this type of diseases.

## BEST DISEASE RESPONSE AT 100 DAYS POST-HSCT \*

*\*If Immunosuppressive treatment only, fill in this section counting 100 days since start of immunosuppressive treatment*

VRTUMRSA2

### **BEST RESPONSE AT 100 DAYS AFTER HSCT OR END OF DEFINITIVE TREATMENT**

See definitions under RESPONSE above.

**Important:** for baseline refer to “STATUS AT TRANSPLANT” (OR STATUS AT LAST IMMUNOSUPPRESSION TREATMENT IF NOT TRANSPLANTED)

Please note that for Severe Aplastic Anaemia sometimes Cyclosporine may continue after the 100<sup>th</sup> day. The Best Response should still be answered, regardless of this.

#### **Med-A only**

VDISESTA

#### **Current disease status**

You must tick only one box. Indicate if the patient is in complete response or not. *The response date is the date that the sample or image was taken for assessing the response*

#### **Date achieved**

If the patient is in CR, enter the date it was achieved or assessed.

#### **Date assessed**

If the patient is not in CR enter the last date the patient's disease status was recorded.

## FORMS TO BE FILLED IN

VTRANTYP

### **TYPE OF HSCT**

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

With extremely few exceptions stem cell transplantations in bone marrow failures are allogeneic or syngeneic transplants. Due to the deficiency of stem cells in bone marrow failures it is difficult to collect a number sufficient for transplantation. Thus, autologous transplantation is not a standard procedure for treatment of bone marrow failures. Only very few cases of autologous transplantation for bone marrow failures have been reported.

Other Please see page 13 **TYPE OF HSCT**

## FOLLOW UP

## BONE MARROW FAILURE SYNDROME

**VRELPROG FIRST RELAPSE OR PROGRESSION AFTER TRANSPLANT**

Relapse of aplasia after bone marrow transplantation is rare, but might happen.  
Report date of onset.

**Criteria for Relapse:**

Deterioration of blood counts with

- return of counts to levels fulfilling criteria of severe aplastic anaemia  
or
- requirement of transfusion in a patient who had achieved a transfusion-independent state before.  
or
- return of counts to levels fulfilling criteria of non-severe aplastic anaemia in patients who had reached complete remission previously  
or
- cytopenia in at least one cell lineage requiring treatment.

**SECONDDI SECONDARY MALIGNANCY DIAGNOSED**

Patients with bone marrow failures are at risk to develop clonal complications like MDS, acute leukaemia or solid tumours. This risk is much higher in patients treated with immunosuppression only as compared to patients who received allogeneic stem cell transplantation.

**VSECTEXT** If secondary malignancy occurs report type of malignancy (tick MDS, AML or free text for any other  
**DISMCLFD** diagnosis) and date of diagnosis.

**VDISESTA DISEASE STATUS AT THIS FOLLOW UP**

Report whether patient is in complete Remission, Partial remission, No response or relapse.  
Criteria for Remission are the same as summarized above.

SPECIFICATIONS  
OF THE DISEASE

## AL AMYLOIDOSIS

## INITIAL DIAGNOSIS

Presents as a plasma cells dyscrasia producing proteins which can damage organs. The AL stands for Amyloid light referring to the light chains.

## EVIDENCE OF UNDERLYING PLASMA CELL DISORDER

**VPLCEDS1** This information is to be found in the patient's file.

If Yes, select the type of disorder:

**Monoclonal gammopathy (MG):**

MG has to be distinguished from MM Stage I. The criteria to diagnose AL amyloidosis with MG are: (1) No osteolysis, (2) Bone marrow infiltration by plasma cells  $\leq 30\%$  and (3) Light-chain excretion in 24-h-urine  $< 1000$  mg/day, (4) monoclonal IgG  $< 30$  g/l.

**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.

**VPLCEDS3**

- **Common type** myeloma means the most usual form, with a complete monoclonal immunoglobulin (M-component) of usually IgG- or IgA-type, 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 by bone marrow sample. '

**VPLCEDS2** **IgG-IgA-IgD-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.

**VPLCEDS4** **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.

**Other B cell malignancy**: AL-amyloidosis can also occur in other disease of B cell origin, e.g. Waldenstrom's disease.

**VSTGDS** **STAGE AT DIAGNOSIS (Salmon and Durie)**

This should only be filled in if there is concomitant Multiple myeloma. The information should be present in the patient's files. Staging is the clinical classification of the severity of the disease at the time of diagnosis, defined as follows:

**Stage I:** Haemoglobin > 99 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).

**VSALMDUR** Add 'A' or 'B' depending on renal function:

- **A** indicates normal or slightly impaired renal function with a serum-creatinine value of < 180 µmol/L,
- **B** indicates more severely impaired function with serum-creatinine = 180 µmol/L.

**DIAGNOSIS OF AMYLOIDOSIS****Methods**

- Amyloidosis must always be confirmed histologically. A biopsy specimen should stain positively with a special staining (Congo-red). Amyloidosis can also occur without evidence of monoclonal gammopathy in a small fraction of patients. Accurate classification may include immunohistochemical staining of tissues. When definitive immunohistochemical typing of amyloid cannot be achieved, specific genetic studies can be performed.
- **Hereditary Amyloidosis:** Were TTR- or other hereditary amyloidoses ruled out by PCR or by immunohistochemistry?
- **Immunohistochemistry:** Was the light-chain type as the causative protein confirmed by immunohistochemistry?

**CLINICAL AND LABORATORY DATA**

**HBD**  
**VBNF** Found in the laboratory printouts in the patient's files. Indicate the values from a date close to the date of diagnosis.

**Bone Marrow Investigations**

**PPLABMD** **BM aspirate, % plasmacytosis:** Indicates the percentage of plasma cells of the total number of nucleated cells in cytologic bone marrow smears.

**PPLABMD** **BM trephine, % plasmacytosis:** 'Trephine' means a special technique for bone marrow biopsy. An examination regarding "amyloidosis of the bone marrow" is also required (congo-red staining).

**SMIGD** **Monoclonal Ig in serum (g/L):** Very important information! A frequently used synonym for monoclonal IG is M-component. Be sure to give the value of the monoclonal Ig: For example, the total IgG in a patient might be 53 g/L, but of this only 48 g might be monoclonal and the remaining 5 g polyclonal; in this situation, the correct figure to indicate in the report is 48.

**UMIGD** **Monoclonal Ig in urine (g/24 hours):** Very important information! Synonyms: Urinary light chains (kappa or lambda chains) or Bence Jones' protein.

**Free light chains in serum (mg/L):** Very important information, if available. This is a relatively new test provided commercially. Additionally to the EBMT criteria it is helpful to assess response after transplantation and is included in the new response criteria for patients with AL amyloidosis.

The presence of a monoclonal serum or urine light chain is helpful but not always sufficient to diagnose a systemic amyloidosis disorder as AL type. All patients require immunofixation electrophoresis of serum (sensitivity 71%) and urine (sensitivity 84%) in an attempt to demonstrate the presence of a monoclonal light chain. Quantification of free light chains is a useful complement to immunofixation, because an abnormal kappa:lambda ratio is seen in 92% of patients. With all 3 assays, the sensitivity is 99% to detect monoclonal gammopathy.

**XBONED**

**Bone structure (X-ray):** Indicates the findings on conventional X-ray, not magnetic resonance tomography or CT scan. For **lytic lesions** it is very hard to give exact definitions of 'minor' and 'major' (e.g. several small lesions could still be minor, but only two large or dangerously localized lesions could be major), so this classification in each individual patient is to be determined by the treating physician; please ask if it is not clearly stated in the patient's notes.

**Typical clinical symptoms**

- Macroglossy
- Periorbital bleeding
- Shoulder pad sign

These are the typical clinical symptoms in patients with AL amyloidosis and mostly not seen in other types of amyloidosis. All 3 criteria belong to soft tissue involvement.

**ORGAN INVOLVEMENT AT DIAGNOSIS: definitions (see also Table 1)**

The seven categories are heart, kidney, liver, nerve, intestine, lung, and soft tissue.

- **Dominant organ involvement**

Most patients have more than 1 organ involved. Often one organ is leading regarding clinical symptoms.

- **Additional organ involvement**

All other involved organs should be listed. It is not necessary to make a biopsy of all organs to diagnose involvement by amyloidosis.

- **No involvement**

There are no clinical symptoms or typical lab values that this organ is involved.

For the completion of the form, the organs in question need to be assessed by the treating physician, using clinical examination and different laboratory methods (see Gertz, A et al, Am J. Hem 2005), and the physician's decision on organ involvement needs to be documented in the patient file.

**TABLE I. Organ Involvement: Biopsy of Affected Organ or Biopsy at an Alternate Site\***

Kidney	24-hr urine protein > 0.5 g/day, predominantly albumin
Heart	Echo: mean wall thickness > 12 mm, no other cardiac cause
Liver	Total liver span > 15 cm in the absence of heart failure or alkaline phosphatase > 1.5 times institutional upper limit of normal
Nerve	Peripheral: clinical; symmetric lower extremity sensorimotor peripheral neuropathy Autonomic: gastric-emptying disorder, pseudo-obstruction, voiding dysfunction not related to direct organ infiltration
Gastrointestinal tract	Direct biopsy verification with symptoms
Lung	Direct biopsy verification with symptoms Interstitial radiographic pattern
Soft tissue	Tongue enlargement, clinical Arthropathy Claudication, presumed vascular amyloid Skin Myopathy by biopsy or pseudohypertrophy Lymph node (may be localized) Carpal tunnel syndrome

\*Alternate sites available to confirm the histologic diagnosis of amyloidosis: fine-needle abdominal fat aspirate and/or biopsy of the minor salivary glands, rectum, or gingiva.

From Gertz et al. Am J Hematol 2005

## ORGAN SPECIFIC DATA AT DIAGNOSIS

### LIVER

Liver span in ultrasound or CT scan

### Heart

NYHA classes:

- Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.
- Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
- Class III: patients with marked limitation of activity; they are comfortable only at rest.
- Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

Left ventricular ejection fraction (%):

Ejection fraction is an important tool in the diagnosis and monitoring of heart failure and certain types of cardiomyopathies. An ejection fraction of less than 40 percent may be present in these conditions. Heart failure occurs when one of the heart's pumping chambers is not pumping well enough to meet the body's needs. Cardiomyopathy is a condition in which the heart is abnormally enlarged, thickened or stiffened.

Interventricular septal wall thickness (mean mm in echocardiography):

In AL amyloidosis with heart involvement a hypertrophy of interventricular septum can be typically observed.

**GASTROINTESTINAL****Weight loss:**

Loss of weight more or less despite adequate nutrition, mostly combined with loss of appetite

**Malabsorption**

Patients with GI involvement often have diarrhoea which leads to a reduced absorption of some components of food, e.g. vitamins, calcium, fat, iron

**GI Bleeding**

GI bleeding is a feared complication of GI involvement. It can occur spontaneously or often after colonoscopy (and perforation) and other interventions.

**Other evidence of GI involvement**

Please describe other symptoms (e.g. gastric ulcer)

**PERIPHERAL NEUROPATHY****PNP severity (NCI grades I-IV)**

Grade 1: Paresthesias and/or loss of reflexes without pain or loss of function

Grade 2: Interfering with function but not with activities of daily living

Grade 3: Interfering with activities of daily living

Grade 4: Permanent sensory loss that interferes with function

**AUTONOMIC NEUROPATHY****Orthostatic hypotension**

Orthostatic hypotension consists of symptoms of dizziness, faintness or light-headedness which appear only on standing, and which are caused by low blood pressure

**Intractable diarrhoea**

This is a severe diarrhoea unresponsive to conventional treatment leading to hypoproteinemia by severe protein losing enteropathy.

**Inflexible pulse rate**

Can be diagnosed in the Holter ECG. The pulse rate is not reacting to the changes of activity of the patient.

**OTHER SITES**

e.g. Faktor X deficiency, arthropathy, skin involvement....

## PRE-HSCT TREATMENT

### VPRETRAT WAS THE PATIENT TREATED BEFORE THE TRANSPLANTATION PROCEDURE

One 'line' of chemotherapy usually consists of repeated cycles of the same type or different type of cycles repeated according to a certain schedule. The term 'line' should not be confused with 'cycle' or 'course' of therapy: For example, initial treatment with four cycles of the VAD-regimen given every fourth week is one line of treatment, i.e. should be indicated under first line therapy, and NOT cycle 1 as first line therapy, cycle 2 as second line therapy etc.

On rare occasions, allogeneic transplantation or stem cell mobilisation followed by autologous transplantation is performed upfront without prior conventional first line therapy. If this is the case, check the **No** box and proceed directly to **Status of disease at start of conditioning** for allogeneic transplantation or to **Status of disease at mobilisation** for autologous transplantation, and on the respective of these latter parts, check the box **At diagnosis** and continue (see below).

**DATF11P** Generally, first line therapy is given. If so, check **Yes** and give approximate **date** for start of treatment, and check appropriate box for modality/modalities.

**VL1REG** Chemotherapy regimen: If any of the most common regimens (VAD, VBAP, VMCP, melphalan-prednisone = MP) has been used, just give the appropriate abbreviation. Otherwise, give the drug names.

Number of cycles: Give the number of cycles of each regimen used.

## HSCT

### TYPE OF HSCT

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

Other Please see page 13 **TYPE OF HSCT**

in extremely rare cases the graft may not fit into either category above. If you have a complex auto/allo case please contact the [Registry Helpdesk](#) first with more details, and they will advise you on how to proceed with your registration.

## STATUS OF DISEASE AT COLLECTION (AUTOGRAFTS ONLY)

Indicates the situation immediately prior to chemotherapy and/or hematopoietic growth factor treatment for mobilisation of hematopoietic peripheral blood stem cells to be used for autologous transplantation. The timing of this procedure should be evident from the notes in the patient file. For the laboratory values pick a date or dates as close as possible before the initiation of this treatment.

**DISSMOBI** **At diagnosis** should be checked if mobilisation treatment was initiated without any other previous first line therapy (see 'First line therapy').

### DEFINITION OF RESPONSE

**Additionally to haematological parameters, organ response is the second part of the evaluation in patients with AL amyloidosis.**

**RSLINE1P**

**Response:** Very important! Please, always fill this part.

The hematologic response criteria for amyloidosis have been modified after those used for multiple myeloma (Table IV). However, the interpretation is more complex than in multiple myeloma. The incidence of pure light-chain proteinemia is much higher than it is in multiple myeloma. Therefore, accurate quantification of a serum monoclonal light chain has been difficult until recently. The high incidence of albuminuria makes accurate quantification of urinary light chain excretion more complicated than it is in multiple myeloma. Often, the monoclonal protein loss is small and comprises only a small percentage of the total urinary protein loss so that accurate serial quantification of the urinary monoclonal protein is fraught with technical problems. The percentage of plasma cells in the bone marrow of AL patients averages approximately 5%, and because these are frequently visual estimates, an accurate confirmation of a reduction that is not attributable to sampling or variability between hematopathologists is difficult. The use of the serum free light chain assay has been important for quantification of hematologic responses and has been proposed as a useful tool to define hematologic response.

**The EBMT-CIBMTR response definitions are applied in patients where the free-light chain test has not been done. In the other patients, the new response criteria (Gertz et al. Am J Hematol 2005; Consensus opinion) should be used as follows:**

**CR (complete remission):** Disappearance of the monoclonal protein from the serum and concentrated urine specimen detected by immunofixation is part of a hematologic response. The number of plasma cells in the bone marrow must be less than 5%, and the serum free light chain ratio becomes normal, supported by a negative immunofixation result. In patients who do not have renal insufficiency, the absolute value of the involved serum-free light chain must also be normal.

**PR (partial remission):** Monoclonal proteins are difficult to quantify accurately below 0.5 g/dL (5 g/L) by serum protein electrophoresis. Because the partial remission criteria are predicated on a 50% reduction in the monoclonal protein, patients who do not have a monoclonal protein greater than 0.5 g in the serum cannot be evaluated quantitatively for response unless there is an abnormal free light chain. Fortunately, patients with AL rarely have an M component in a polyclonal Background.

**A partial remission is defined by a greater than 50% reduction in the value of the serum monoclonal protein when measurable and a 50% reduction in 24-hr urine monoclonal light chain excretion when measurable.** To be measurable, the urine light chain excretion must exceed 100 mg/day and a definable band must be seen on urine protein electrophoresis. A discrete band is uncommon in renal amyloidosis patients, and urine M-protein reductions are easiest to quantify in cardiac or neuropathic amyloidosis. If the serum and urine monoclonal protein do not fulfil the criteria for measurable disease, they are considered evaluable only and can be coded only as present or absent. Patients without a quantifiable M component are the ones in whom the serum-free light chain measurement is the most valuable. A 50% reduction in the serum free light chain concentration has been demonstrated to have important survival value and is associated with clinically improved organ function. A 50% reduction in the involved serum free light chain is considered evidence of a partial hematologic (immunochemical) remission. However, the initial pre-treatment serum-free light chain value should be greater than 10 mg/dL (100 mg/L) for it to be considered measurable. Although the normal value for the free light chain is 3–4 mg/dL, values that are only slightly above this can decrease into the normal range because of laboratory variation. It is recommended that light chain values below 10 mg/dL (100 mg/L), although abnormal, not be considered a criterion for evaluation of hematologic response. Variations in reagent lots and methods may affect results for patients who are monitored serially and can compromise the test's clinical utility.

**MR (minor response):** The category of minor response has not been defined for amyloidosis as it has for multiple myeloma.

## DEFINITION OF RELAPSE AND PROGRESSION

**Relapse from CR:** reappearance (immunofixation) of the original monoclonal protein in the serum or urine or an increase in the serum free light chain from the normal range into the abnormal range. For the serum-free light chain, the increase must be at least a doubling from the normal range to be considered progression. An increase from 3 to 4 mg/dL would not be considered progression (owing to laboratory variation); rather, a doubling to at least 76 mg/dL would be required for progressive disease. Immunofixation is an important adjunct to confirm that the change in the free light chain concentration is related directly to reappearance of the monoclonal protein.

**Progression from PR:** Hematologic progression is evidenced by a 50% increase in the amount of the monoclonal protein from its lowest measured value. To avoid coding progression owing to laboratory variation, the increase

in the serum monoclonal light chain must be greater than 0.5 g/dL (5 g/L) by electrophoresis, and the 50% increase in urinary light chain must be greater than 200 mg/day. In addition, there should be a concomitant increase in the serum free light chain concentration of 50%, and this must increase to a value greater than 10 mg/dL (100 mg/L) for coding progression. The percentage of bone marrow plasma cells is not included in the partial remission or progression criteria. The low number of plasma cells in most patients and the difficulty in accurately concluding when a 50% increase or decrease in the percentage of plasma cells has actually occurred make this an inadequate measure of response **CR2** indicates that the patient has been in first CR after first or second line therapy, then relapsed and eventually was put in a second CR by second/third line therapy, respectively, which means that if CR2 is checked, CR must also be the last treatment response checked at second or third line treatment for everything to be coherent.

**VINTRAT Plateau** This is defined for all patients who do not achieve a complete or partial remission and do not fulfil the criteria for progressive disease.

A plateau is frequently not awaited in patients planned for a transplantation, e.g. the patient is treated with a fixed number of first line chemotherapy cycles until the monoclonal immunoglobulin/urinary light chain value fulfils the criterion for PR in one single value (the lowest value available), and the patient then proceeds directly to the next treatment step, i.e. stem cell mobilisation. In this frequent case, check the box '**Unknown**' for plateau.

This question is not applicable for '**Non-secretory**' myeloma.

**VSERIMMF Immunofixation of serum / urine**

**VGMINF** For patients in CR, it is very important to indicate whether this CR was determined by the more sensitive method of **Immunofixation** of serum or urine, or by the older, less sensitive, standard electrophoresis method. If CR has been determined by immunofixation, check '**Negative**' in the appropriate slot for urine and / or serum. If CR has been determined by electrophoresis and immunofixation has not been performed, check '**Unknown**'.

If patient is not in CR, and immunofixation has been performed it will be '**Positive**'. Information on whether immunofixation has been done or not should be indicated on the appropriate laboratory report for protein analysis in the patient file. If still uncertain, ask the treating physician who should know whether immunofixation is done in the laboratory of the respective hospital.

**TABLE IV. Hematologic (Immunochemical) Response Criteria**

Complete response	Serum and urine negative for a monoclonal protein by immunofixation Free light chain ratio normal Marrow < 5% plasma cells
Partial response	If serum M component > 0.5 g/dL, a 50% reduction If light chain in the urine with a visible peak and >100 mg/day and 50% reduction If free light chain >10 mg/dL (100 mg/L) and 50% reduction
Progression	From CR, any detectable monoclonal protein or abnormal free light chain ratio (light chain must double) From PR or stable response, 50% increase in serum M protein to > 0.5 g/dL or 50% increase in urine M protein to > 200 mg/day; a visible peak must be present Free light chain increase of 50% to >10 mg/dL (100 mg/L)
Stable	No CR, no PR, no progression <sup>a</sup>

<sup>a</sup>CR, complete response; PR, partial response.

**ORGAN STATUS:** The organ response criteria have been defined for the main organ involvement as described below.

**HEART RESPONSE AND PROGRESSION**

A symptomatic improvement of 2 New York Heart Association classes without increase in diuretic need is suggestive of cardiac improvement, if wall thickness has not increased. Progression of cardiac disease can be defined as an increase of 2 mm or more in wall thickness compared with baseline. The ejection fraction in amyloidosis is usually preserved until late in the disease, and changes in this variable are insensitive for assessing disease progression. However, worsening of congestive heart failure strongly suggests progression of cardiac disease even if wall thickness remains unchanged.

**Kidney response and progression**

A 50% decrease in 24-hr urine protein excretion (predominantly albumin) in the absence of a 25% increase of the serum creatinine concentration (minimum of 0.5 mg/dL) or a 25% decrease in creatinine or iothalamate clearance constitutes a response (Tables II and III). The reduction in urinary protein loss must also be greater than 0.5 g for the response criteria to be fulfilled. This is to avoid coding a response due to variations in the urinary protein collections. Because 24-hr urine protein measurements can vary substantially within the same patient, some caution is required to avoid coding a random fluctuation as a response. Progression of amyloidosis in the kidney is defined by a 50% increase in the urinary protein excretion. The absolute increase, however, should be greater than 1 g/day to avoid coding progressive disease when an increase represents a random fluctuation (ie, the urinary protein increase from 500 to 800 mg would not constitute progression because the absolute change, 300 mg, is less than 1 g). A 25% worsening of serum creatinine (minimum of 0.5 mg/dL) or creatinine clearance constitutes evidence of progression independent of urinary protein loss. Patients who do not fulfil the criteria for progressive disease or responsive disease are considered stable.

**Liver response and progression**

A reduction in the size of the liver documented by radiographic or radionuclide imaging is important. The craniocaudal liver scan (computed tomographic or ultrasonographic) is useful (Tables II and III). The span can decrease by greater than 30% 1 year following stem-cell transplantation in responders. A decrease in the alkaline phosphatase value represents the primary measure of hepatic response. In patients who have hepatic involvement, the alkaline phosphatase abnormality should decrease by 50%. In other words, if the institutional normal value is 100 U/L, and the patient's alkaline phosphatase value is 200 U/L, it must decrease below 150 U/L to be considered a hepatic response. Progression is defined as an increase of greater than 50% above the lowest recorded value. If the institutional normal value for alkaline phosphatase is 100 U/L, and the patient's alkaline phosphatase value is 160 U/L, then a value of 240 U/L is required to reflect progressive disease. Right-sided heart failure can produce modest changes in alkaline phosphatase concentration. Recognition of this phenomenon is necessary when interpreting outcomes.

**Nervous system response and progression**

Assessment of response and progression in the nervous system is difficult because of the lack of objective means of measuring response (Tables II and III). The electromyogram is relatively insensitive in detecting improvement in nerve conduction, although frequently it can document progressive disease with involvement of other nerves as well as further slowing of nerve conduction velocity. With current therapy, reversal of amyloid peripheral neuropathy is uncommon and is often difficult to separate from supportive measures used to treat the neuropathy (i.e., gabapentin or amitriptyline).

**Soft tissue response and progression**

It is unusual to see a reduction in the size of the tongue with any form of systemic therapy (Tables II and III). Likewise, resolution of claudication symptoms or normalization of skeletal pseudohypertrophy or periarticular soft tissue amyloid is rare. Computed tomography and magnetic resonance imaging have been used to assess soft tissue changes.

**Pulmonary response and progression**

Radiographic evidence of improvement in pulmonary interstitial amyloid is rare (Tables II and III). Radiographs are useful, as are computed tomographic studies of the lungs, to demonstrate change. Corticosteroids can have an important impact on gas exchange, and the use of the diffusing capacity of carbon monoxide is not a reliable serial measure of improved lung function because it requires a high level of patient compliance and can be affected by steroids and the patient's cardiac status.

**TABLE II. Organ Response**

Heart	Mean interventricular septal thickness decreased by 2 mm, 20% improvement in ejection fraction, improvement by 2 New York Heart Association classes without an increase in diuretic use, and no increase in wall thickness
Kidney	50% decrease (at least 0.5 g/day) of 24-hr urine protein (urine protein must be > 0.5 g/day pretreatment) Creatinine and creatinine clearance must not worsen by 25% over baseline
Liver	50% decrease in abnormal alkaline phosphatase value Decrease in liver size radiographically at least 2 cm
Nerve	Improvement in electromyogram nerve conduction velocity (rare)

**TABLE III. Organ Disease Progression**

Heart	Interventricular septal thickness increased by 2 mm compared with baseline An increase in New York Heart Association class by 1 grade with a decreasing ejection fraction of $\geq 10\%$
Kidney	50% increase (at least 1 g/day) of urine protein to greater than 1 g/day or 25% worsening of serum creatinine or creatinine clearance
Liver	50% increase of alkaline phosphatase above the lowest value
Nerve	Progressive neuropathy by electromyography or nerve conduction velocity

## STATUS OF DISEASE AT START OF CONDITIONING FOR BMT

**DISSCOND** To be completed in all patients. For details, see previous explanations in this manual.

### HEMATOLOGICAL STATUS; ORGAN STATUS; CLINICAL AND LABORATORY DATA

See same section under **STATUS OF DISEASE AT COLLECTION**

**ORGAN INVOLVEMENT AT TRANSPLANT:** this has to be filled in again. There could be a large time span between diagnosis, first treatment and transplant. In that time new organ involvement could be occurred.

See same section under **ORGAN INVOLVEMENT AT DIAGNOSIS**

## STATUS OF DISEASE AT 100 DAYS AFTER TRANSPLANTATION

**TUMRSA2** For response definitions see previous applicable parts of this mini-manual.

**Date of CR:** Very important. Give date if CR was reached at the time of the report.

### Med-A only

#### Current disease status

You must tick only one box. Indicate if the patient is in complete remission or not.

For baseline refer to "STATUS AT TRANSPLANT"

#### Date achieved

If the patient is in CR, enter the date it was achieved or assessed.

#### Date assessed

If the patient is not in CR enter the last date the patient's disease status was recorded.

### Evidence of new organ involvement:

Patients should be checked at each time of follow-up if there are new clinical symptoms consistent with organ involvement of new sites.

## FORMS TO BE FILLED IN

### **VTRANTYP** TYPE OF HSCT

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

Other Please see page 13 **TYPE OF HSCT**

## FOLLOW UP

## AL AMYLOIDOSIS

### **TUMRSA2** COMPLETE REMISSION OBTAINED?

**VDATECR** Very important! In this type of disease, complete remission may not be seen until after 100 days have relapsed since transplant. For this reason, the question is repeated in the follow up form. If CR, it is also very important to give the date. If the exact date cannot be retrieved, please make an approximation.

SPECIFICATIONS  
OF THE DISEASECHRONIC LYMPHOCYTIC LEUKAEMIA  
(AND OTHER LEUKAEMIAS)

Chronic lymphocytic leukaemias (CLL) are malignancies of the mature lymphocyte. The normal lymphocytes can be divided into two main groups: B lymphocytes and T lymphocytes. B lymphocytes make antibodies (immunoglobulins) and T lymphocytes are cells that can kill foreign cells (e.g. virus infected cells or allogeneic transplants). Depending on their origin, chronic lymphocytic leukaemias are therefore divided into B-cell and T-cell types. General characteristics of this group of diseases are lymphocytosis ( $> 5 \times 10^9/L$ ) and enlarged lymph nodes and spleen.

The classification in the MED-AB forms shows chronic lymphocytic leukaemias subdivided into: CLL/SLL, B-PLL, T-PLL, Richter's syndrome, Hairy cell leukaemia and Atypical Hairy cell leukaemia.

## INITIAL DIAGNOSIS

## SUBCLASSIFICATION

*This is very important information. Please, always try to fill in this section even if certain information around diagnosis is missing.*

## Chronic Lymphocytic Leukaemia (CLL) / Small Lymphocytic Lymphoma (SLL)

CLL is the most common form of adult leukaemia in the Western world. Most patients are over 60 years of age and for this reason may not be eligible for a 'traditional' allogeneic or autologous transplantation. With conventional chemotherapy no cure can be reached. The disease has an indolent course and survival is between 5 and 15 years. However, a minority of patients may suffer from a more aggressive course with early resistance to standard chemotherapy, in particular fludarabine or other purine analogues, and short survival. The diagnosis is made both by distinct morphology and distinct immunophenotype. Cytogenetics are more important for establishing the prognosis.

Chronic Lymphocytic Leukaemia (CLL) and Small Lymphocytic Lymphoma (SLL) are the same in all characteristics with the exception of the percentage of malignant cells in the bone marrow. In contrast to CLL, SLL has no (or only few) malignant cells in the bone marrow and peripheral blood.

T-CLL does no longer exist in the latest WHO classification. The cases formerly classified as T-CLL now have to be considered as T-PLL. CLL is now always considered to be a B-cell disease.

**Clinical features:** The patient mostly presents with a high leukocyte count and a heavily infiltrated bone marrow. In advanced stages, haematopoiesis is supplanted by lymphocytes, resulting in a decrease of Hb, granulocytes and platelets. Anaemia, infections and bleeding are the consequences. Additional complications of leukemic cell proliferation may be the development of auto-immune phenomena, especially auto-immune haemolytic anaemia (AIHA), and immune thrombocytopenia (ITP). Finally, indolent CLL can transform into an aggressive lymphoma, such as diffuse large cell lymphoma or Hodgkin's disease. This is called "Richter's transformation" (see below) and is associated with a poor prognosis under conventional therapy. Many cases are diagnosed when a routine blood test is performed. With physical examination, usually enlarged lymph nodes as well as hepatosplenomegaly are found.

## T-PLL

T-PLL stands for T-cell prolymphocytic leukaemia and is characterised by high and rapidly growing peripheral counts of monoclonal T-cells with a characteristic CD4+ immunophenotype in the absence of lymph nodes and cutaneous lesions. It is a very rare leukaemia. The disease is mostly insensitive to chemotherapy and the prognosis is unfavourable within a few years. The diagnosis is made on morphologic characteristics and on immunophenotype.

## B-PLL

B-PLL stand for B-cell prolymphocytic leukaemia and is also a very rare leukaemia. The disease is mostly insensitive to chemotherapy and the prognosis is unfavourable within a few years. The diagnosis is made on

morphologic characteristics and on immunophenotype. Sometimes the discrimination between CLL and B-PLL may be difficult.

### Richter's syndrome

"Richter's syndrome" denotes the transformation of CLL into an aggressive lymphoma, such as diffuse large cell lymphoma or Hodgkin's disease. Richter's transformation can occur primarily (i.e. as the first manifestation of a CLL) or during the course of a typically indolent CLL. However, in every case the underlying disease is CLL. Richter's syndrome is associated with a poor prognosis under conventional therapy.

#### Transformed from a previously known CLL

Although Richter's syndrome must occur together with a CLL, sometimes the diagnosis of CLL was not previously known at the time of Richter's diagnosis. In those cases, answer "No: Primary Richter" to the "Disease of secondary origin or transformed" question in the database.

If a CLL was clearly diagnosed previously, answer "Yes" to the "transformed" question. If transformed from CLL, please also indicate the date of the original CLL diagnosis. ProMISe users will be asked for this original CLL diagnosis if answering "Yes" to "Disease of secondary origin or transformed"

In both cases, Richter's would be the main indication diagnosis.

#### VCLLSUBC

### Hairy Cell Leukaemia (HCL)

HCL is always of B-cell origin. The morphology and the immunophenotype is very characteristic but most of the patients are not leukaemic but pancytopenic (low haemoglobin, low leukocyte count, low platelet count) which makes the diagnosis not always easy. Usually, the patients do not present with enlarged lymph nodes, but they do have a large spleen. Most of the patients have a 'dry tap' at diagnosis, which means that you cannot find a result (laboratory form) of the bone marrow aspirate, check -in this case- the bone marrow biopsy form. Long remissions can be obtained with conventional treatment. The disease is rare and candidates for transplantation are even more unique.

### Atypical Hairy Cell Leukaemia

The cells in Atypical HCL are more "punk" than "hairy" in morphology and they differ also in immunophenotype. The disease is very rare and the clinical course is much more unfavourable than the true HCL.

#### VCPLSUBC

Check the letter with which the patient was referred from another hospital or the pretransplant letter/summary of your transplant department for the subclassification of the CLL (or PLL). The official possibilities are CLL (or SLL if aleukaemic); T-PLL; B-PLL; Richter's syndrome; HCL, and Atypical HCL. These diagnosis are mutually exclusive (i.e. there can be only one diagnosis (CLL or B-PLL or T-CLL etc.). The only exception is Richter's syndrome which must occur together with a CLL (see above for advice on how to enter this diagnosis).  
B-cell

### CYTOGENETICS

See cytogenetics form or ask cytogenetics team.

#### VCHROMOS

#### Technique

#### CYTOGTCH

"Conventional" cytogenetic technique is a chromosomal analysis for which dividing cells are required (=metaphases). Typically around 32 cells are analysed with this type of technique.

In CLL it is difficult to stimulate cells to divide (as opposed to Acute Leukaemia cells), therefore, a technique like FISH (Fluorescent In Situ Hybridization) is frequently used. This method analyses non dividing cells (*cells in interphase*) and investigates about 400 cells.

#### CHRMABND

#### Abnormalities

Cytogenetic abnormalities should be reported for CLL and PLL.

In CLL, the most common cytogenetic abnormalities are deletions and trisomies, like 13q- (= del 13 q14) or trisomy 12. Translocations in CLLs are uncommon. The most important abnormality in the context of transplant, however, is deletion 17p- (= del 17p13), also referred to as "p53 lesion", since this defect is associated with a strongly impaired prognosis under standard therapy and indicates an allogeneic transplant indication per se. For results see cytogenetics form and consult your physician.

#### VCHRXNRD

If you find translocation (11;14), please ask your supervisor whether the diagnosis of Mantle-Cell lymphoma has been considered (and excluded).

**VH gene status**

The VH gene status refers to the particular conformation of the immunoglobulin gene of the leukemic CLL B- cells. There are two basic possibilities for the VH gene status: “Unmutated” (denoting a poor prognosis) and “Mutated” (denoting a favourable prognosis). Some times the cut-off assay value for differentiating between “unmutated” and “mutated” is mentioned, which usually is “98% homology”. Since patients with “mutated” VH usually have a good prognosis except for those whose CLL cells’ immunoglobulin gene uses the VH family “VH3-21”, the presence or absence of this marker can help to further characterise the prognosis of patients with “mutated” CLL.

The VH status is important for CLL (including Richter’s) only and therefore usually not available for T-PLL, B-PLL, and the HCLs.

**MOLEBIO****MARKERS**

ZAP70 is an intracellular protein which is expressed in strong correlation with the VH gene status, i.e. unmutated patients should be ZAP70+ and mutated patients ZAP70-. There are, however, exceptions from this rule. ZAP70 is still not standardized. Therefore the cut-off value used to differentiate between negative and positive should be given (mostly 20% positive cells).

**VMARKERS**

Other Marker: detected, for example, by FISH or other cytogenetic technique.  
If other markers are used, please describe the abnormalities.

**VPIMMCD4****IMMUNOPHENOTYPING**

Immunophenotyping should be reported for T-cell PLL.

**CLINICAL STATUS AT DIAGNOSIS****Lymphocyte count****LYMPHOC**

Report the lymphocyte count for PLL only

**DOUBTIME**

**Lymphocyte doubling time** refers to the interval of time it takes for lymphocyte counts to double; it is a prognostic factor but rarely used nowadays. Fill it in only if it is clearly stated in the file (mostly it is not). A short doubling time (less than one year) of the leukocyte count is unfavourable

**CLLBINET****Binet stage**

In Europe, CLL is clinically graded using a staging system developed by Binet et al. Some investigators prefer the Rai staging system which largely corresponds to the Binet system as depicted below. Both systems try to predict survival by basal clinical assessment. Please note that both Binet and Rai Staging systems apply for CLL only and must not be used for the other diagnoses covered by this MedB form.

(Please refrain from drawing ‘staging-conclusions’ yourself. This overview is meant to be used as background information)

Stage	Clinical feature	Corresponds to Rai stage
A	haemoglobin $\geq 10$ g/dL * platelet count $\geq 100.0\mu\text{L}$ < 3 areas involved	0-II
B	haemoglobin $\geq 10$ g/dL * platelet count $\geq 100.0\mu\text{L}$ $\geq 3$ areas involved	I-II
C	haemoglobin < 10 g/dL * <b>or</b> platelet count < 100.0 $\mu\text{L}$	III-IV

## PRE-HSCT TREATMENT

### VPRETRAT TREATMENT BEFORE THE HSCT PROCEDURE

**VCHEMOTH** Chemotherapy usually consists of a series of cycles of the same or different type which are repeated according to a certain schedule (= "chemotherapy regimen"). The agents contained in the regimen used must be listed in the space left after "Yes: Regimen". Dose information is not requested. If available, acronyms instead of the full list of components can be provided for commonly used regimens (e.g. "FC", "FC-R", "CHOP", "R-CHOP", "FluCam" etc).

The term 'treatment' should not be confused with 'cycle' or 'course' of therapy: For example, initial treatment with four cycles of the VAD-regimen given every fourth week is **one** treatment with **four** cycles. Do NOT specify cycle 1 as first line therapy, cycle 2 as second line therapy etc.

For transformed diseases e.g. Richter's Syndrome as indication for transplant, you should register the pre-HSCT treatment (and response/status) given since the transformation, rather than the original CLL.

### TUMRSA2 Response:

[Adopted from the new IWCLL/NCI guidelines, Hallek et al, Blood Jan 23 2008]

After any of the above therapies, the response definitions are as follows:

#### CR\* (complete remission):

Absence of clonal lymphocytes in the peripheral blood and absence of significant lymphadenopathy (e.g. lymph nodes greater than 1,5 cm in diameter) and absence of hepatomegaly or splenomegaly and absence of constitutional symptoms.

#### PR (partial remission):

To define a PR, **at least one** of the following parameters needs to be documented for a minimal duration of 2 months

- A decrease in the number of blood lymphocytes by below 50% or more from the value prior to therapy;
- A decrease in lymph node size by below 50% or more in the sum products of up to 6 lymph nodes, or in one lymph node diameter if only a single lymph node was present prior to therapy, without increase in any lymph node, and no new enlarged lymph node;
- A decrease in the size of the liver and/or spleen by 50% or more as defined by CT scan, palpation, or ultrasound.
- The blood count should show one of the following results if abnormal prior to therapy: Polymorphonuclear leukocytes at 1,500/ $\mu$ L or more or 50% improvement over baseline without G-CSF support; platelet counts greater than 100,000/ $\mu$ L or 50% improvement over baseline; haemoglobin greater than 11.0 g/dL or 50% improvement over baseline without transfusions or erythropoietin support.

#### Progression (PD):

Progressive disease is defined by **at least one** of the following:

- Lymphadenopathy: progression of lymphadenopathy occurs, if one of the following events is observed:
  - Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
  - An increase by 50% or more in greatest determined diameter of any previous site.
  - An increase of 50% or more in the sum of the product of diameters of multiple nodes.
- An increase in the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B-cells per  $\mu$ L.
- Transformation to a more aggressive histology (e.g. **Richter's syndrome**).
- Occurrence of cytopenia (neutropenia, anaemia or thrombocytopenia) attributable to CLL.

**No change:** Patients who have not achieved a CR or a PR, and who have not exhibited progression, will be considered to have no change (which is equivalent to a non-response).

\*This definition of CR refers to *clinical* response, NOT included are results obtained by immunophenotyping, cytogenetics and/or molecular biology. These techniques are more sensitive and if CR is defined using one of these techniques it needs to be clearly specified (e.g., immunological CR, molecular CR etc.).

## DISEASE STATUS AT HSCT

IDAABC

### DATE OF HSCT

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.

VSPLECNE

### Splenectomy

Splenectomy means the removal of the spleen via a diagnostic laparotomy. If this has been done, please indicate the date.

### DISEASE STATUS

See above for definitions of response. (N.B. “Nodular PR” does no longer exist according to the 2008 IWCLL/NCI Guidelines)

### RESIDUAL DISEASE STATUS (ONLY TO BE COMPLETED, WHEN PATIENT IS IN HAEMATOLOGICAL CR)

Immunological and molecular biological investigations are more sensitive in detecting leukaemic cells than morphological or clinical methods (physical examination, CT scans, etc.). With these techniques residual cells may be found even when the patient fulfils the criteria for haematological CR (see above).

#### Minimal residual disease (MRD)

VMFACPCR

*investigated by* FACS (Fluorescence-Activated Cell Sorting)

(look for the *conclusion* in the reports)

VMBCELIM

*investigated by* Immunophenotyping

(look for the *conclusion* in the reports)

VMOBCEMB

*investigated by* Molecular Biology (PCR)

(look for the *conclusion* in the reports)

**Sensitivity** of MRD assays denotes the capacity of the assay to detect CLL cells among normal cells in blood or bone marrow samples. According to the 2007 International Standard, it is expressed as “%”: 1% means 1 CLL cell in 100 normal cells; 0.1% means 1 CLL cell in 1000 normal cells etc. Accepted MRD assays for CLL should have a sensitivity of 0.01% or better.

#### Worst Binet stage up to and including this date

See definitions above, at diagnosis

### BIOLOGICAL RISK FACTOR ASSESSMENT

#### CYTOGENETICS

##### Abnormalities

##### VH gene status

See definitions above, at diagnosis

### HAEMATOLOGICAL VALUES

HBD

Hb stands for haemoglobin (the conversion factor for Hb in mmol/L to g/dL is 1.61)

A Bone Marrow aspirate is used to investigate the cytological aspects of separate cells, a trephine-biopsy investigates the Bone Marrow as tissue (architectural structure of the marrow).

ASPPCLYM

BM aspirate: % lymphocytes ..... (an accurate count)

PCLYMPHC

BM trephine: % lymphocytes ..... (usually an estimate)

If the examination of the BM aspirate is done by the haematologist, look for the result in the haematology form. The examination of the trephine (the biopsy) is done by the pathologist, so the result can be found on the pathology form.

**CLINICAL DATA**

<b>VLMPHAD</b>	Lymphadenopathy:	see physical examination form at diagnosis or letter from the referring centre. It can be: cervical, axillary and inguinal lymphadenopathy (uni or bilateral), spleen and liver*
<b>VLNOG</b>	Number of lymph node sites	fill in the individual number of lymph node sites* affected, based on physical examination (e.g. right axilla, left axilla etc) * Areas of involvement are: (1) cervical lymphnodes, (2) axillary lymphnodes, (3) inguinal lymphnodes, (4) liver and (5) spleen
<b>VTHABCTS</b>	Thoraco abdominal CT scan	see radio diagnostic form
<b>SPLMEGB</b> <b>HEPMEGB</b>	Spleen size and liver size	If only a physical examination has been done, please mention the centimetres below costal margin. If an ultrasound or CT scan has been done, please mention the largest diameter (in centimetres)

**Purine analogue-refractory?**
☐ No    ☐ Yes    ☐ Unknown

(non response or relapse within 6 months after completion of purine analogue- containing chemotherapy)

Refractoriness to purine analogues is an important prognostic factor in CLL (not in the other diseases covered by this MedB form) and should therefore be recorded. It is defined by non-response or relapse **within 6 months** after end of regimens which contains purine analogues. Purine analogues are fludarabine, cladribine (2-CDA), and pentostatin. Examples for purine analogue-containing regimens are FC, FC-R, F-R, PC-R, cladribine etc.

If the patient has not been treated prior to the HSCT, this question should be skipped.

**Early relapse after intensive therapy?**
☐ No    ☐ Yes    ☐ Unknown

(within 24 months after completion of purine analogue-containing combination therapy or autologous SCT)

Early relapse after intensive therapy is another prognostic factor in CLL (not in the other diseases covered by this MedB form) and should therefore be recorded. It is defined by relapse **within 24 months** after end of a regimens which contains purine analogues plus other agents, such as cyclophosphamide, rituximab etc.. Examples are FC, FC-R, F-R, PC-R, cladribine etc.

If the patient has already been described as being Purine analogue-refractory or if the patient has not been treated prior to the HSCT, this question should be skipped.

## ADDITIONAL TREATMENT POST-HSCT

**ADDITIONAL DISEASE TREATMENT**
☐ No

☐ Yes: ☐ Planned (planned before HSCT took place)

☐ Not planned (for relapse/progression or persistent disease)

Please specify whether or not additional treatment was given. Also specify whether this treatment had been planned as part of the original transplant protocol (Planned) or whether it is a reaction to an event (or lack of an expected event, ie: obtaining a CR) that has taken place in between the transplant and this follow up (Not planned).

For example, rituximab is disease treatment in the case of a CLL.

If rituximab is given as maintenance and this has been decided prior to the transplant being performed then it is "planned".

If rituximab is given for a CLL relapse which happened after the transplant then it is "not planned". This is true, even if the rituximab is the standard treatment for a relapse and, as such, it could be said that there was a plan to treat the patient with rituximab if the patient relapsed or if the patient did not respond to the HSCT.

Additional cell therapies are not reported here. In both MED-A and MED-B, cell infusions are included elsewhere in the forms. Second transplants should not be reported in Additional Disease Treatment either: please complete a new MED-A or MED-B for additional transplants.

## BEST DISEASE RESPONSE AT 100 DAYS POST-HSCT

PLEASE SEE : 'DISEASE STATUS AT HSCT'

### Med-A only

#### Best disease status (response) after HSCT

You must tick only one box. Indicate if the patient is in complete remission or not.

For baseline refer to "STATUS AT TRANSPLANT"

*The response date is the date that the sample or image was taken for assessing the response*

#### Date achieved

If the patient is in CR, enter the date it was achieved or assessed.

#### Date assessed

If the patient is not in CR enter the last date the patient's disease status was recorded.

### VTRANTYP

#### TYPE OF HSCT

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

Other    Please see page 13 **TYPE OF HSCT**

## FOLLOW UP

## CHRONIC LYMPHOCYTIC LEUKAEMIA

## VRELPROG

## FIRST EVIDENCE OF RELAPSE OR PROGRESSION SINCE LAST HSCT

- ☐ Previously reported
- ☐ No
- ☐ Yes, date diagnosed

..... - ..... - .....

yyyy mm dd

As a general rule, confirmation of complete remission by the specified methodology must have been done before the relevant type of relapse can be considered.

Definitions for CLL relapse:

## VRELLEUK

**Haematological relapse**

Cytological and/or histological evidence of the disease in the marrow-blood and/or in extramedullary sites (lymphnodes, spleen, liver, CNS, testis, skin, etc) in a patient who was until now in complete remission. Immunophenotypic and/or molecular confirmation of the presence of the disease is recommended.

**Haematological progression**

Progressive disease is defined by **at least one** of the following:

- Lymphadenopathy: progression of lymphadenopathy occurs, if one of the following events is observed:
  - Appearance of any new lesion such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly or other organ infiltrates.
  - An increase by 50% or more in greatest determined diameter of any previous site.
  - An increase of 50% or more in the sum of the product of diameters of multiple nodes.
- An increase in the liver or spleen size by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B-cells per  $\mu\text{L}$ .
- Transformation to a more aggressive histology (e.g. **Richter's syndrome**).
- Occurrence of cytopenia (neutropenia, anaemia or thrombocytopenia) attributable to CLL.

**MRD relapse**

Detectable MRD after having achieved MRD negativity once before. It should not be assessed prior to day +100 since its prognostic value early after transplant is low.

**MRD progression**

MRD progression is more difficult to assess and requires a quantitative MRD detection assay, such as MRD-flow or RQ-PCR. The definition of progression depends on the assay used and is largely assay specific.

## LAST DISEASE AND PATIENT STATUS

## VDISESTA

**DISEASE STATUS**

Complete Remission	no evidence of disease on physical examination, haematological laboratory values and bone marrow morphology.*
Stable disease	< 25% increase of lymphnode sizes <u>and/or</u> elevation of WBC
Relapse	(see above for haematological relapse)
Progression	(see above for haematological progression)

\* This is the definition of a *clinical* disease status, NOT included is immunophenotype, cytogenetics or molecular biology. These techniques are more sensitive and if CR is defined using one of these techniques it needs to be clearly specified (e.g., immunological CR, molecular CR etc.).

**RESIDUAL DISEASE STATUS**

Please see definitions under DISEASE STATUS AT HSCT.

SPECIFICATIONS  
OF THE DISEASE

## CHRONIC MYELOID LEUKAEMIA

Chronic Myeloid Leukaemia (CML) is an infrequent neoplastic disease (incidence 1 to 2 /100 000 population/year). It is a remarkable blood cancer and the first ever discovered (1840). It is also the first neoplastic disease where chromosomal abnormalities were shown to be a consistent feature, and its later molecular alterations the unique cause of the first phase of the disease. The chromosomal abnormality is a translocation or movement between chromosome 9 and 22 denoted as t(9;22) ("Philadelphia chromosome", shortened as "Phi"). This t(9;22) abnormality is easily detectable in the vast majority (>95%) of patients with CML by cytogenetic analyses and FISH. Only a minority of patients has a t(9;22) negative ("phi-") CML when testing and this is most probably due to lack of sensitivity of the test.

After 1980 it was clear that the translocation caused two distinct genes (the BCR and ABL genes) to fuse into one fusion gene called BCR-ABL, which produces a protein called BCR-ABL. This protein has tyrosine-kinase activity and induces profound disturbances in the regulation of proliferation, apoptosis (cell death) and in the interactions with the extracellular matrix.

The BCR-ABL gene might be present even if no t(9;22) abnormality is detectable on cytogenetic analysis. The disease has a chronic phase lasting years, an accelerated phase lasting months and a blast crisis (similar to an acute leukaemia) which is the usual cause of death. The blast crisis can be myeloid or lymphoid. In about 70% of the cases of blast crisis, the blast lineage is myeloid, and may include neutrophilic, eosinophilic, basophilic, monocytic, erythroid or megakaryocytic blasts, or any combination thereof. In approximately 20-30% of patients, the blast crisis is due to proliferation of lymphoblasts. The blast lineage may be obvious on morphologic grounds, but often the blasts are primitive or heterogeneous. For this reason immunophenotypic analysis is recommended. Myeloid blasts may have strong, weak or no myeloperoxidase activity but will have antigens associated with myeloid, monocytic (CD13, CD14, CD15, CD33, etc.), megakaryocytic (CD41a, CD61) and/or erythroid (glycophorin A, haemoglobin) lineages. Not uncommonly the myeloid blasts will express one or more lymphoid antigens. Most cases of lymphoblastic blast crisis are precursor B lymphoblasts (positive for CD22, CD19, and TdT but negative for surface Ig) but cases of precursor T-cell origin (positive for CD3 and TdT) may also occur. In many cases of lymphoid blast crisis, one or more myeloid antigens can be co expressed on the blasts. Rarely, lymphoid and myeloid lineage blasts are present simultaneously.

After successful treatment a patient can return to a previous phase, called then, for example, second chronic phase.

Drugs in frequent use today for the treatment of CML are hydroxyurea, interferon, Imatinib (Glivec ), Nilotinib (Tasigna) and Dasatinib (Sprycel). In the past busulphan was commonly used and splenic irradiation was also given.

## INITIAL DIAGNOSIS

**VCMLSUB SUBCLASSIFICATION** *THIS QUESTION MUST BE ALWAYS ANSWERED*

Check the letter with which the patient was referred from another hospital or the pretransplant letter/summary of your transplant department for the subclassification of the CML.

CML could have the translocation t(9;22) present or absent (very rare) but all CML cases have the bcr-abl gene present (if the translocation t(9;22) has been detected the test for the presence of bcr-abl gene may not be necessary to confirm the diagnosis and subclassification).

**VDISESTA STATUS OF DISEASE AT DIAGNOSIS**

The status of the disease **at diagnosis** (whether it is Chronic Phase, Accelerated Phase or Blast Crisis), is usually written in the pretransplant letter. If not, check the patient's notes.

**We recommend the use of the WHO criteria** (World Health Organization Classification of Tumours. Pathology & Genetics. Tumours of the haematopoietic and lymphoid tissues. Page 20-26. Please look at <http://www.iarc.fr/WHO-bluebooks/> for information on how to order the book.)

- Chronic Phase: none of the features of accelerated phase or blast crisis
- Blast Crisis: any one of the following:
  - Blasts  $\geq 20\%$  of peripheral blood white cells or of nucleated bone marrow cells
  - Extramedullary blast proliferation
  - Large foci or clusters of blasts in the bone marrow biopsy
- Accelerated Phase: any one of the following:
  - Blasts 10-19% of WBC in peripheral blood and/or nucleated bone marrow cells
  - Peripheral blood basophiles  $\geq 20\%$
  - Persistent thrombocytopenia ( $< 100 \times 10^9/L$ ) unrelated to therapy
  - Persistent thrombocytosis ( $> 1000 \times 10^9/L$ ) unresponsive to standard therapy
  - Increasing spleen size and increasing WBC count unresponsive to standard therapy
  - Cytogenetic evidence of clonal evolution

## CYTOGENETICS AND MOLECULAR DATA AT DIAGNOSIS

IDAABECC

### Translocation (9;22)

For t(9;22) positive CML, fill in this section.

PCMETAPH

METAPHEX

% Translocation (9;22) metaphases (*dividing cells*): Please mention here the percentage of the metaphases with the translocation. The number of metaphases examined is important because if the metaphases that were seen are less than 20, the percentage of the t(9;22) positive cells is unreliable.

FISHANA

VFISHPCP

FISH (Fluorescent In Situ Hybridisation) is another cytogenetic technique that is frequently used.

Where "conventional" cytogenetic investigation is performed on dividing cells (*metaphases*), FISH can also analyse non-dividing bone marrow cells (*cells in interphase*) and investigates about 400 cells, thus many more than the cells that are analysed with "conventional" cytogenetic analysis.

VBCRABLD

**Molecular Analysis bcr-abl.** *BCR-ABL* is the fusion gene found within the chromosomal abnormality, t(9;22). In this case, its presence is determined with a molecular biological technique. This (RNA) technique goes further and investigates *genes* instead of *chromosomes*. This time the translocation is not named after the chromosomes (numbers 9 and 22) that are involved in the translocation, but after the genes (*BCR* on chromosome 22 and *ABL* on chromosome 9), which are positioned together as a result of the translocation. The molecular analysis can be performed by PCR (Polymerase Chain Reaction) or by FISH. PCR is much more sensitive. If either of these techniques was used, please indicate whether the results were 'positive' or 'negative'. If molecular analysis was not performed, tick the corresponding box.

Note that it is possible to have a positive molecular test in the presence of a negative cytogenetics investigation, which may be not as sensitive as the PCR.

VCHROMOS

### CYTOGENETICS OTHER THAN FOR TRANSLOCATION (9;22) AT DIAGNOSIS

The cytogenetic abnormalities can be characterised as changes involving chromosome number (ploidy) or chromosome structure (translocation, inversion). Please check the cytogenetics result form and consult your physician on how to classify possible other **abnormalities**.

VMETAPEX

CHRMABN

Number of metaphases with abnormalities. Number of metaphases examined.

this gives important information on the percentage of metaphases with anomalies and is always given in the results of the cytogenetic analysis. It is essential information to know the accuracy of the results.

**HAEMATOLOGICAL VALUES AT DIAGNOSIS****Peripheral blood**

**HBD** Hb stands for haemoglobin (g/dL). If your laboratory provides the results in mmol/L, the conversion factor for Hb in mmol/L to g/dL is 1.61.

**ETC.** Example: xx.x mmol/L x 1.61 = yy.yy g/dL

**Bone marrow**

**PBLBMD** % blasts. Can be found in a bone marrow aspirate laboratory result (not in the bone marrow “histology / biopsy” form).

**SPLMEGD** Palpable Splenomegaly The spleen size is usually mentioned in the pretransplant summary or in the letter from the referring centre.

**VSPLEEND** If only a physical examination has been done, please mention the centimetres below costal margin.

**VSPLCTSC** If an ultrasound or CT scan has been done; please mention the largest diameter (in centimetres) (In case of a discrepancy between the maximum diameters obtained by ultrasound **and** CT scan, report the maximum diameter obtained by ultrasound examination.)

## PRE-HSCT TREATMENT

**Patient treated before HSCT**

**VPRETRAT** Hydroxyurea and Imatinib are common CML treatments after diagnosis. If these, or other drugs were given, like for instance, Interferon, ARA C (cytosine arabinoside), Dasatinib or Nilotinib), and you are reporting using the Med-B form, please add the first and last date of treatment for each drug. If you are reporting using the Med-A form, dates are not requested.

It is important for the Working Party to know whether a Tyrosine Kinase receptor antagonist was given or not, which is why in Promise there is the option 76. **Tyrosine kinase receptor antagonist, any**, to which if you answer No to the question “Drug or regimen given”, you are stating that there was none given.

If the drug is not listed, use Other and specify the drug clearly.

**VCHEMOTH** [To enter the data in ProMISe, choose the very first date of all dates written on the form in this section to create the treatment record.]

## HSCT DATE and TYPE

**DATE OF HSCT**

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.

**VSPLECNE** **Splenectomy**

**DATSPLEC** Splenectomy means the removal of the spleen via a diagnostic laparotomy. If this has been done please indicate the date.

**VTRANTYP** **TYPE OF HSCT**

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic            the patient receives stem cells from another person  
Autologous        the patient receives his/her own stem cells back

Other    Please see page 13 **TYPE OF HSCT**

## REASTRAN

**REASON FOR THE HSCT**

Check pretransplant letter or ask your physician. Select what is considered the main reason, and tick all other reasons that you think may also be relevant as secondary.

Clonal evolution means that in the cytogenetic analysis there is at least one new chromosomal abnormality (or several) in addition to the t(9;22). In other words, at diagnosis there was only the t(9;22) abnormality and after a while a new alteration in the chromosomes has occurred. It is not a phase of the CML; however, in many cases development of clonal evolution is a criterion to classify the CML as accelerated. Also, it predicts for the development of a more advanced phase (accelerated or blastic phase) in the near future.

ABL mutations are changes in the normal composition of the ABL gene (the correct names is "point mutations"). In CML there is no need for ABL to have any mutations. It is simply "attached" to another gene, called BCR, forming a mega gene (fusion gene) called BCR-ABL. But both genes (BCR and ABL) remain unchanged or unmutated despite being attached together. During treatment with Imatinib and other tyrosine kinase inhibitors (TKIs) it is relatively frequent to develop one or more mutations in the ABL gene (which of course, continues to be attached to the BCR gene). Mutations are important because in many cases they make the BCR-ABL resistant to the therapeutic effects of Imatinib and other TKIs.

Other: use this to indicate non listed reasons like, for example, "Patient's preference"

## STATUS OF DISEASE AT MOBILISATION ONLY IF AUTOGRAFT

## STATUS OF DISEASE AT HSCT

## VDISESTA

## VNUMSTM

**PHASE (NUMBER AND REMISSION STATUS)**

***We recommend the use of the WHO criteria*** (World Health Organization Classification of Tumours. Pathology & Genetics. Tumours of the haematopoietic and lymphoid tissues. Page 20-26. Please look at <http://www.iarc.fr/WHO-bluebooks/> for information on how to order the book.)

- Chronic Phase: none of the features of accelerated phase or blast crisis
- Accelerated Phase: any one of the following :
  - Blasts 10-19% of WBC in peripheral blood and/or nucleated bone marrow cells
  - Peripheral blood basophiles  $\geq 20\%$
  - Persistent thrombocytopenia ( $< 100 \times 10^9/L$ ) unrelated to therapy
  - Persistent thrombocytosis ( $> 1000 \times 10^9/L$ ) unresponsive to standard therapy
  - Increasing spleen size and increasing WBC count unresponsive to standard therapy
  - Cytogenetic evidence of clonal evolution
- Blast Crisis: any one of the following symptoms :
  - Blasts  $\geq 20\%$  of peripheral blood white cells or of nucleated bone marrow cells
  - Extramedullary blast proliferation
  - Large foci or clusters of blasts in the bone marrow biopsy

## VBLASTC1

*If blast crisis:*

The blast crisis can be myeloid or lymphoid or other (for instance erythroblastic, megakaryoblastic or mixed) depending on the morphology and the immunophenotype.

## VNUMSTM

**NUMBER**

This number is mainly relevant for chronic phase (CP). A patient can only be in the next chronic phase after he has experienced blastic phase (blast crisis) or accelerated phase.

Number the different phases chronologically with one exception: if a patient presents at diagnosis in accelerated phase or blast crisis, you must assume that prior to the presentation there must have been a period of chronic phase which went undetected. **Therefore, when a patient presenting in accelerated phase or blast crisis is restored (by whatever means) to chronic phase, this must be CP2.**

**REMISSION STATUS**

The following definitions should be used for type of remission,

**VREMTRAN** Haematological remission - all of the following:

- WBC < 10 x 10<sup>9</sup> /L
- Haemoglobin > 11.0 g/dL
- Platelet Count < 500 x 10<sup>9</sup> /L
- Normal Differential (<1% precursor cells)
- No palpable splenomegaly
- No extramedullary disease

**VCYTOGRE** Cytogenetic remission (complete) 0% t(9;22) positive metaphases together with haematological remission  
*NOTE: A minimum of 20 analysable metaphases must be assessed for appropriate evaluation of a cytogenetic remission. Remission should be confirmed with repeated cytogenetic analysis within 4 to 12 weeks*

Note: A patient in cytogenetic remission must be in haematological remission but could still present a molecular relapse. This is because the cytogenetic technique has a higher resolution than haematological measurements but lower resolution than molecular methods

**VMOLECR** Molecular remission cells with the BCR/ABL fusion protein are not detectable, in the peripheral blood and /or the bone marrow, by an assay with a sensitivity to allow detection of one t(9;22) positive cell in 10<sup>5</sup> to 10<sup>6</sup> RT-PCR cells. The result should be confirmed by two consecutive tests done at least 4 weeks apart.

Note: A patient in molecular remission must also be in cytogenetic and haematological remission. This is because molecular techniques have a higher resolution than both haematological and cytogenetic measurements.

**IDAABECC CYTOGENETICS/MOLECULAR STATUS AT HSCT**

**VFISHANA** See under CYTOGENETICS/MOLECULAR STATUS AT DIAGNOSIS, above, on how to fill in this section.

**IDAABECC** **Translocation (9;22)** Fill in only if patient is not in cytogenetic remission.

**PCMETAPH** % Translocation (9;22) metaphases (*dividing cells*): Please mention here the percentage of the metaphases with the translocation. The number of metaphases examined is important because if the metaphases that were seen are less than 20, the percentage of the t(9;22) positive cells is unreliable.

**FISHANA** FISH (**F**luorescent **I**n **S**itu **H**ybridisation) is another cytogenetic technique that is frequently used.

**VFISHPCP** Where “conventional” cytogenetic investigation is performed on dividing cells (*metaphases*), FISH can also analyse non-dividing bone marrow cells (*cells in interphase*) and investigates about 400 cells, thus many more than the cells that are analysed with “conventional” cytogenetic analysis.

For the Additional cytogenetic analysis? you only need to fill in whether it has been done and whether it is abnormal or not.

**VBCRABLD** **Molecular Marker BCR-ABL.** Fill in only if patient is not in molecular remission.

*BCR-ABL* is the fusion gene found within the chromosomal abnormality, t(9;22). In this case, its presence is determined with a molecular biological technique. This (RNA) technique goes further and investigates *genes* instead of *chromosomes*. This time the translocation is not named after the chromosomes (numbers 9 and 22) that are involved in the translocation, but after the genes (*BCR* on chromosome 22 and *ABL* on chromosome 9), which are positioned together as a result of the translocation. The molecular analysis can be performed by PCR (Polymerase Chain Reaction) or by FISH. PCR is much more sensitive. If either of these techniques was used, please indicate whether the results were ‘positive’ or ‘negative’. If molecular analysis was not performed, tick the corresponding box.

BCR-ABL result, etc.

If the test is positive, fill in the results. The number of copies BCR-ABL could be anything between zero and one million (or more). The same applies for the control gene. This control gene is one of the thousands of normal genes that we all have and could be a different one in each lab. Examples of control genes include ABL, G6PDH, BCR, B2-Microglobulin and others. ABL is the preferred one in the current international standardisation project. The BCR-ABL/control gene ratio is simply the division of the number of copies of the BCR-ABL gene divided by the number of copies of the lab’s control gene. It is usually expressed as a percentage (without units), so you need to multiply the ratio by 100.

Note that it is possible to have a positive molecular test in the presence of a negative cytogenetics investigation, which may be not as sensitive as the PCR.

### HAEMATOLOGICAL VALUES AT HSCT

HBD  
ETC

Look for laboratory results on a date as close as possible but before the start of the conditioning regimen (TBI and/or chemo). See above, under HAEMATOLOGICAL VALUES AT DIAGNOSIS for further explanations

VESTRMBP  
VFOCIBM

### Large foci or clusters of blasts in BM / Extramedullary blast proliferation

According to WHO criteria, blast crisis may be diagnosed also in the absence of marrow blasts  $\geq 20\%$  in the bone marrow aspirate when an extramedullary blast proliferation (\*) and/or large foci or clusters of blasts in the bone marrow biopsy are present.

(\*) ie. *cytologically and/or histologically proven growth of blast cells, in tissue other than peripheral blood or bone marrow.*

SPLMEGB  
VSPLEEND

### Palpable Splenomegaly

See same section at diagnosis

## ADDITIONAL DISEASE TREATMENT

- ☐ No  
☐ Yes: ☐ Planned (*planned before HSCT took place*)  
☐ Not planned (*for relapse/progression or persistent disease*)

Please specify whether or not additional treatment was given.

For example, Imatinib is disease treatment in the case of CML. If Imatinib is given as maintenance then it is "planned"; if Imatinib is given for CML relapse then it is "not planned".

Additional cell therapies are not reported here. Second transplants should not be reported here: please complete a new MED-A or MED-B for additional transplants.

## DISEASE STATUS AT DAY +100 POST HSCT

.... AND ... AT EACH FOLLOW-UP.

The definition of disease status after transplant for CML is complex, as the presence of the disease can be defined at haematological, cytogenetic and molecular levels. If all these tests are performed at regular intervals it is possible to see patterns of remission and relapse emerging. However many centres do not perform all these tests at regular intervals and then it is difficult to see, for instance, whether a patient is progressing at the molecular and/or cytogenetic levels.

We recommend that the assessment of disease status by all three parameters (haematological, cytogenetic and molecular) is performed at three monthly intervals for the first year after transplant and at 6 monthly intervals thereafter, unless the disease status is changing or treatment has been initiated, in which case more frequent assessments may be indicated.

This may not be always possible, in which case it is necessary to maintain consistency within your centre with respect to the nature and frequency of testing and to define the best response of a patient post transplant. Any subsequent analyses can then be compared to this best response, or if treatment has intervened, to the response at the previous follow-up.

Definitions of molecular, cytogenetic and haematological remission are the same as in the section REMISSION STATUS, above. For baseline refer to "STATUS AT TRANSPLANT"

## FOLLOW UP

## CHRONIC MYELOID LEUKAEMIA

This section will only deal with items for which it is felt that CML specific explanations are necessary. For all other more general questions, please see the **GENERAL FOLLOW UP** chapter.

**ADDTREAT DISEASE TREATMENT****VADLYMPH Cell infusion (CI)**

Lymphocytes are frequently transfused to achieve remission of the disease in patients with CML relapse after an allogeneic stem cell transplant. Such transfusions may be repeated after transplant with various intervals and cell doses. Note that TCL (T-cell lymphocytes) infusion is just a type of DLI and should be reported as such. In addition donor CD34+ve cells may be transfused in case of myelosuppression (ie. neutropenia and/or thrombocytopenia) after donor lymphocyte transfusion. Therefore it is important that the date and the cell dose of each transfusion of donor cells are reported Also; please specify any occurrence of GvHD after DLI.

**Other treatment**

See explanation **ADDITIONAL DISEASE TREATMENT** at HSCT above.

Stopping/tapering of immunosuppression is when after the SCT and in order to treat the relapse of CML, the patient stops or quickly reduces the immunosuppressive drugs (for example, cyclosporine A), which are otherwise given routinely for several months. This is one of the possible treatments for relapse. It is not always possible to stop/reduce the immunosuppression (for example, if active GVHD is still present).

Report all treatment given with the corresponding dates. If all treatments cannot be listed in the given space, please print the page as many times as necessary and fill in details for all treatments.

**VRELPROG FIRST RELAPSE OR PROGRESSION AFTER TRANSPLANT**

☐ Previously reported

☐ Yes, date of relapse/progression

..... \* ..... \* .....  
dd mm yyyy

**VRELLEUK Haematological relapse**

Cytological and/or histological evidence of the disease in the marrow-blood and/or in extramedullary sites (CNS, testis, skin, etc) in a patient considered to have been in haematological remission. Indicate the 1<sup>st</sup> date it was noted. Cytogenetic and/or molecular confirmation of the presence of the disease is recommended unless any change in current therapy was performed because of the relapse.

Chronic phase, blast crisis or accelerated phase. Please see the description at **STATUS OF DISEASE AT HSCT**; however, exclude Cytogenetic evidence of clonal evolution for accelerated phase

**VRELLEU3 Cytogenetic relapse**

presence of one or more t(9;22) positive metaphases with standard cytogenetics or hypermetaphase FISH and/or >2% cells with the BCR/ABL fusion gene by interphase FISH, in a patient lacking any evidence of the disease at haematological/clinical level. Indicate the 1<sup>st</sup> date it was noted; this may be different from the date of haematological relapse.

NOTE: a patient can be in cytogenetic relapse and still appear to be in haematological remission. This is because cytogenetic techniques have a higher resolution than haematological measurements and will detect abnormalities earlier.

**VRELLEU5 Molecular relapse**

Presence of cells with the BCR/ABL fusion protein by an assay with a sensitivity to allow detection of one t(9;22) positive cell in 10<sup>5</sup> to 10<sup>6</sup> cells in a patient lacking any other evidence of the disease (ie. haematological remission and cytogenetic CR). Results must be confirmed >30 and <90 days after the 1<sup>st</sup> positive assay unless any change in current therapy was performed because of the 1<sup>st</sup> positive assay. Cytogenetic CR and

haematological CR must also be confirmed by a second assay. In any case, the date of relapse is the date of 1<sup>st</sup> positive assay and should be indicated; this may be different from the date of haematological and cytogenetic relapse.

NOTE: a patient can be in molecular relapse and still appear to be in haematological or cytogenetic remission. This is because molecular techniques have a higher resolution than haematological or cytogenetic measurements and will detect abnormalities earlier.

It is possible to have a cytogenetic or molecular relapse while not being in haematological relapse. The reason for this is because the haematological tests are the least sensitive of all.

#### Sites of relapse

Relapse of CML is most commonly detected in the peripheral blood and bone marrow, but occasionally it may be detected in extramedullary sites. Extramedullary relapse usually occur concomitantly with relapse in the marrow or blood, but it may also occur without haematological evidence of relapse. In the latter case molecular relapse is usually detected in the blood or the marrow.

Extramedullary localisations most commonly involve the skin, lymph node, bone or central nervous system, but can occur anywhere. Extramedullary localisations may behave clinically as an organomegaly (lymph node localization), a growing tumour (ie. skin localisation), an inflammatory disease (ie. meningeal localisation) or an effusion (ie. pleural localisation). Clinical symptoms are frequently not specific of leukemic relapse, thus the diagnosis has to be confirmed on bioptic material from the affected tissue. In case of a relapse in blast crisis localisations may be of myeloid or lymphoid lineage.

## DISEASE AND PATIENT STATUS ON DATE LAST SEEN

### LAST DISEASE STATUS

The definition of disease status after transplant for CML is complex, as the presence of the disease can be defined at the haematological, cytogenetic and molecular levels. If all these tests are performed at regular intervals it is possible to see patterns of remission and relapse emerging. However many centres do not perform all these tests at regular intervals and then it is difficult to see, for instance, whether a patient is progressing at the molecular and/or cytogenetic levels.

We recommend that the assessment of disease status by all three parameters is performed at three monthly intervals for the first year after transplant and at 6 monthly intervals thereafter, unless the disease status is changing or treatment has been initiated, in which case more frequent assessment may be indicated. This is not always possible, in which case it is necessary to maintain consistency within your centre with respect to the nature and frequency of testing and to define the best response of a patient post transplant. Any subsequent analyses can then be compared to this best response, or if treatment has intervened, to the response at the previous follow-up.

Definitions of molecular, cytogenetic and haematological remission are the same as in the section REMISSION STATUS, above. Definitions of accelerated phase and blast crisis are the same as in the section STATUS OF DISEASE AT HSCT with the exception of Cytogenetic evidence of clonal evolution which is NOT a criterion for accelerated phase after transplant.

### DEATH

#### Cause of death

If a patient dies in remission (ie. complete haematological remission, or cytogenetic remission, or molecular remission) because of toxic effects of treatments given after transplant to treat or to prevent relapse, tick **Treatment related** and specify the treatment and the cause of death.

All other items asked in the follow-up have been defined above or in the GENERAL FOLLOW UP chapter of this manual.

SPECIFICATIONS  
OF THE DISEASE

## HAEMOGLOBINOPATHY

## PRIMARY DISEASE

Haemoglobinopathies are a heterogeneous group of inherited diseases characterised by alteration of haemoglobin production. Adult haemoglobin is composed of 2  $\alpha$  and 2  $\beta$  chains (tetramer  $\alpha_2\beta_2$ ). Lack of production of  $\beta$  chains characterises  $\beta$  thalassemia, lack of production of  $\alpha$  chains characterises  $\alpha$ -thalassemia (which in homozygous condition is not compatible with life).

Sickle Cell Disease is a congenital disease characterised by the production of an altered haemoglobin. *Sickle Cell Gene* is a point mutation gene and the disease is due to the homozygosis of this gene.

## VHEMOGLO DIAGNOSIS

Main haemoglobinopathies treated with stem cell transplantation are:

Beta thalassemia major  
Sickle cell Disease  
Compounded heterozygosis

## THALTYPE

- **$\beta$  Thalassemia major** is the inheritance of two thalassemic genes (more than 100 thalassemic mutations have been identified). This condition causes a life-threatening anaemia from the first years of life. Patients can only survive through receiving red blood cell transfusions. If a patient requires regular chronic blood transfusions the form is called Cooley's anaemia. If a patient requires occasional transfusions, or is able to maintain an acceptable haemoglobin value, it is called Thalassemia intermedia. Cooley's anaemia and thalassemia intermedia are clinical terms; for both conditions the molecular defect is homozygous thalassemia. Thalassemia minor is a healthy condition characterised by the presence of a single thalassemia gene (thalassemia trait, thalassemia bringer etc.). These patients have a normal life with a very mild anaemia.
  - $\beta$  thalassemia major is divided into two groups on the basis of absence ( $\beta^0$ ) or a presence ( $\beta^+$ ) of  $\beta$  chains in the peripheral blood
- **Sickle Cell Disease (SCD)** (synonym: Sickle cell anaemia, phalciform anaemia, drepanocytosis) is a hereditary disease characterised by the presence of an altered haemoglobin (haemoglobin S = Hbs). Anaemia is not always present. Patients experience pain episodes involving different organs. They are due to sickling phenomena and are a cause of major morbidity of the disease, such as brain involvement and stroke. The course of the disease is often unpredictable.

## VSICKLPC

- **Compound heterozygosis** (synonymous microdrepanocytosis) is due to the presence of a thalassemic gene associated with a Sickle Cell Disease gene. The disease is heterogeneous and often more similar to SCD but sometimes with a clinical pattern similar to that of thalassemia major.  $\beta^s$  % indicates the percent of haemoglobin S in the peripheral blood.

Other forms of haemoglobinopathies are characterised by the inheritance of a thalassemia gene or an SCD gene associated with other less frequent pathological haemoglobin (for example haemoglobin E)

Haemoglobinopathies are clinically progressive diseases. This section describes the main clinical characteristics at the time of transplant. They constitute the staging of the disease.

## PRETRANSPLANT BIOLOGICAL FEATURES

### Molecular defect

Any haemoglobinopathy can be fully defined by molecular diagnosis. This will be implemented soon in the database (for example COD39/IVS101, COD39/COD39) but for the time being we just want to know whether the test has been done.

## PRETRANSPLANT MAIN CLINICAL FEATURES

This section reports clinical characteristics typical of thalassemia (gonadal dysfunction, substitutional hormonal therapy, growth impairment) or SCD (all the others) or both.

Indicate if the complication was present at the moment of pre-transplant evaluation (yes, no or data is not available).

**SPLMEGB** Splenomegaly / Hepatomegaly

**HEPMEGB** The spleen/liver size is usually mentioned in the pretransplant summary or in the letter from the

**VSPLEEMD** referring centre. Indicate the centimetres below costal margin.

**VDIABETE** Diabetes

Indicate the presence of diabetes and whether it is or not insulin dependent.

**VHGCLF1** OTHER CLINICAL ABNORMALITIES INDICATING THE SEVERITY OF THE PRIMARY DISEASE

...2 There may be other less frequent complications related to the disease (for example severe bone

...3 deformity). Please give details here.

**CODISDES** MAJOR DISEASES NOT RELATED TO THE TREATMENT OF HEMOGLOBINOPATHY

There may be additional complications NOT related to the disease (for example other congenital abnormalities). Please give details here.

## **VCHELAT** CHELATION TREATMENT PRETRANSPLANT

Thalassemia patients (and SCD patients if treated with chronic blood transfusions) require continuous chelation (treatment with an iron chelating agent, usually Deferoxamina and in the last few years oral chelator Deferiprone).

Please indicate if the patient received chelation and whether the chelation was regular or not. Definition of regular chelation for deferoxamina is “regular subcutaneous continuous infusion started within 18 months from the first transfusion and continued at least 5 days/week for the rest of their life”. Irregular is any failure to obtain this standard. This section is essential for Risk class definition.

**IDAABC** Indicate the date the patient started chelation.

## STATUS OF DISEASE AT TRANSPLANT

This section includes other important clinical characteristics determined at pre transplant evaluation.

### DATE OF TRANSPLANT

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.

**VSPLECNE** Splenectomy means the removal of the spleen via laparotomy.

**PATPRTRF** RBC Transfusions means packed red blood cell transfusions. The age (in months) at the first transfusion and the total number of transfusions received (in the patient's lifetime) are required as part of the pre-transplant evaluation.

**LDHD** When reporting the enzyme and other biochemical values, ensure you use the correct units. Conversion  
**VASTVAL** tables are available if the laboratory reports the values in different units. If the substance has not been  
**ALTSGPT** analysed, indicate by ticking on the **Not evaluated** box.  
 .....

**VVCARDIA** **CARDIAC FUNCTION:** indicate if the patient has a clinical history of cardiac disease and whether they have received corresponding treatment.

**LIVDISE** **LIVER FUNCTION:** indicate positivity for HBV, HCV or other viruses. For HCV indicate serology (presence of anti-HCV antibodies) and viremia (PCR = polymerase chain reaction for HCV, positive or negative). It is possible to indicate other viruses under: Other  
**VOTHLIV**

Enzymes: indicate results of laboratory examination before conditioning regimen

### Liver biopsy

**LIVBIOP** A cornerstone of thalassemia disease staging. Data must be reported from the pathology examination of the liver sample.

**VHEPATIT** Hepatitis: inflammatory liver disease. Chronic hepatitis is reported as persistent or active, do not consider other definitions ("reactive", "aspecific").

**BIOPRES** Siderosis: iron accumulation in the liver. Iron is determined in the histology section after Prussian blue coloration (Perls reaction). There are several histology scores to determine iron. In this section simply state if iron is present and if iron accumulation is mild, moderate or severe.

**VFIBORIS** Fibrosis: (collagen deposition) fibrosis is the stage of liver disease. Even in this case there are several fibrosis score systems (Knodel, Ishak, Metavir). Report if fibrosis is present (yes or no). Staging is indicated by fibrosis without bridging, bridging fibrosis and cirrhosis. These categories can be completed using the histology and fibrosis scores.

**CLASS** **CLASS**  
 Conclusion of the pre transplant evaluation.

## FORMS TO BE FILLED IN

**VTRANTYP** **TYPE OF HSCT**  
 Only allogeneic transplants are performed for genetic diseases. Please proceed to the ALLOGRAFT form.

Allogeneic            the patient receives stem cells from another person

Other    Please see page 13 **TYPE OF HSCT**

## FOLLOW UP

## HAEMOGLOBINOPATHY

**CAUSE OF DEATH** *(check only one main cause)*

Primary disease related cause *(check as many as appropriate)*

If the patient dies as a consequence of the haemoglobinopathy, it is important to know which complication associated to this disease was the most likely cause of death. Check as many causes as necessary (for example HCV related Cirrhosis and hepatocarcinoma or iron related cardiac disease)

## PATIENT STATUS AT THIS FOLLOW UP

Haemoglobinopathies are non-malignant diseases. The concept of relapse is not applicable in this setting. The evolution of engraftment is however very important.

VSYSTAL  
VREASTR

**DISEASE STATUS**

Indicate whether the patient undergoes regular transfusions. If no, indicate the chimaerism status.

Full engraftment = 95% donor cells

Mixed chimera = coexistence of donor and patient cells.

Chimaerism is diagnosed by:

Cytogenetic (or FISH= **F**luorescent **I**n **S**itu **H**ybridization) for Y chromosome (if donor and patient are sex mismatched)

Chromatography: production of  $\beta$  chains

Molecular biology: donor DNA

and results should be looked at in the corresponding laboratory sheets.

If transfusions are required it means there has been loss of allo engraftment and autologous reconstitution (100% patient cells).

All other items asked in the follow-up have been defined above or in the “General follow up” section of this manual.

SPECIFICATIONS  
OF THE DISEASE

## LYMPHOMA

## INITIAL DIAGNOSIS

Lymphomas are malignant neoplasms of the lymphatic system, which includes lymph nodes, spleen, thymus, Waldeyer's ring, appendix, and Peyer's patches. Lymphomas are divided into two subgroups: Hodgkin lymphoma (HL) and Non Hodgkin lymphomas (NHL).

**Hodgkin lymphoma** has a monoclonal origin with B-lymphocytes being involved in most cases. At an early stage only lymphnodes are affected, at an advanced stage it is a systemic disease that might as well affect extralymphatic organs (bone marrow, liver). Ratio male: female is 3 to 2. In Europe and the USA there are two age peaks: one around 30 and one above 60 years old. It is assumed that there is a connection in some cases between EBV infection and pathogenesis of Hodgkin lymphoma. Typical symptoms are: swelling of lymph nodes without pain (60% cervical, 30% mediastinal, 20% axillar, 15% both abdominal or inguinal) - few patients describe painful lymphnodes after consumption of alcohol; fever, night sweats, weight loss, and hepatosplenomegaly. The laboratory results often show elevated ESR and LDH values, anaemia, and typical lymphocytopenia.

**Non Hodgkin lymphomas** have the tendency to grow discontinuously in the lymphatic system and it can involve the extralymphatic system more often than HL. Thus, the gastrointestinal tract, the liver, the bone marrow, and the peripheral blood are affected much more often than in Hodgkin's disease. Ratio male : female = 1.5 : 1. About 2/3 of the patients with NHL are between 50 and 80 years old. Patients with AIDS have got a 1000 times higher incidence of NHL. Typical symptoms are: swelling of lymph nodes, fever, night sweat, weight loss, skin affection. The bone marrow is affected in 50% of cases, thus, the laboratory results often show: anaemia, thrombocytopenia, and leucocytopenia.

**WHOLYCLS WHO SUBCLASSIFICATION**

☐ **Non Hodgkin Lymphoma (NHL)**

☐ **Hodgkin Lymphoma**

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 and T- and NK-cell lymphomas are in separate sections on the form.

The exact diagnosis has to be given in the pretransplantation letter or in the description given by the 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 many years ago follow these earlier classifications.

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 contact [Registry Helpdesk](#) for further advice.

**VSECORIG Transformed from another type of lymphoma**

☐ No ☐ Yes ☐ Unknown

In some cases, the lymphoma is a transformation from a previous and different type of lymphoma (ex. follicular lymphoma may transform to a diffuse large B-cell lymphoma). In this case, tick "Yes" here.

**I PROINDEX PROGNOSTIC INDEXES, GRADE AND SCORING SYSTEMS**

A number of prognostic indexes are used for different types of lymphoma. These indexes use the presence of known risk factors to assess the prognosis of the patient. In addition, some of the indexes are calculated with a correction according to the age of the patient. Please, use the correct one as noted on the forms specific lymphomas.

**Grade**

Grade is determined by morphology and is incorporated in the WHO description of the disease. Grade is assessed differently for each type of lymphoma.

Please, provide the grade for Follicular and Mantle cell lymphomas. The information should be in the patient's notes.

**International Prognostic Scoring System for Waldenström macroglobulinemia (ISSWM)****Risk factors**

Age > 65 years
Haemoglobin $\leq$ 11.5 g/dL
Platelet count $\leq$ 100 x10 <sup>9</sup> /L
Serum B2-microglobulin > 3 mg/L
Serum monoclonal protein > 70 g/L

**Risk category**

0 or 1 risk factor (except age >65)	Low
Any 2 risk factors or age >65 alone	Intermediate
> 3 risk factors	High

[International prognostic scoring system for Waldenström macroglobulinemia](#). Morel P et al. Blood 2009; 113: 4163-4170.

**Follicular lymphoma International Prognostic Index (FLIPI)****Risk factors**

Age > 60 years
Disease at stage III or IV
more than four lymph node groups involved
Haemoglobin < 12.0 g/dL
Elevated serum LDH

**Risk category**

0 or 1 risk factor	Low
Any 2 risk factors	Intermediate
> 3 risk factors	High

[Follicular lymphoma international prognostic index](#). Solal-Céligny. P et al. Blood. 2004 Sep 1;104(5):1258-65. Epub 2004 May 4.

**International Prognostic Index (IPI)**

This index is to be used for patients with aggressive NHL (mostly DLBCL) regardless of the age at diagnosis.

**Risk factors**

Age > 60
Disease at stage III or IV
More than 1 extranodal site
ECOG performance status 2, 3 or 4
Elevated serum LDH

**Risk category**

0 or 1 risk factor	Low
Any 2 risk factors	Low-intermediate
Any 3 risk factors	High-intermediate
> 3 risk factors	High

[A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project.](#)

N Engl J Med. 1993 Sep 30;329(14):987-94.

In addition to the indexes or scores, the **Proliferation index** is also requested for some types of lymphoma, more specifically for mantle cell lymphoma (MCL). This index is an indication of the number of malignant cells that are dividing, and uses the levels of the KI-67 protein to assess it.

[A new prognostic index \(MIPI\) for patients with advanced-stage mantle cell lymphoma.](#) Hoster E et al. German Low Grade Lymphoma Study Group (GLSG); European Mantle Cell Lymphoma Network. Blood. 2008 Jan 15;111(2):558-65. Epub 2007 Oct 25. Erratum in: Blood. 2008 Jun 15;111(12):5761.

**VSTGDST****STAGE AT DIAGNOSIS**

This information will be in the patients file.

The Ann Arbor staging is used for all adult patients. The Murphy stage is used for all paediatric and all Burkitt's disease patients. The ISCL/EORTC stage is used for staging Mycosis fungoides and Sezary syndrome.

*Ann Arbor staging*

<b>Stage I</b>	one area of lymph nodes is affected. It includes:
stage Ie:	localised involvement of one non-lymphatic organ
<b>Stage II</b>	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 OR localised involvement of one or more non-lymphatic organs on the same side of the diaphragm
<b>Stage III</b>	groups of lymph nodes on <u>both</u> sides of the diaphragm have been affected. It includes:
stage IIIe:	groups of lymph nodes on <u>both</u> sides of the diaphragm have been affected PLUS one localised involvement of one non-lymphatic organ
Stage IIIs:	groups of lymph nodes on <u>both</u> sides of the diaphragm have been affected PLUS the spleen
<b>Stage IV</b>	diffuse or disseminated involvement of one or more non-lymphatic organs with or without involvement of lymph nodes.

*Murphy staging (paediatric NHL)*

<b>Stage I</b>	single tumour (extranodal) or single anatomic area (nodal), with the exclusion of mediastinum or abdomen
<b>Stage II</b>	single tumour (extranodal) with regional node involvement two or more nodal areas on the same side of the diaphragm two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm

	primary gastrointestinal tract tumour, usually in the ileocecal area, with or without involvement of associated mesenteric nodes only, grossly completely resected
<b>Stage III</b>	two single tumours (extranodal) on opposite sides of the diaphragm two or more nodal areas above and below the diaphragm all the primary intrathoracic tumours (mediastinal, pleural, thymic) all extensive primary intra-abdominal disease, unresectable: all paraspinal or epidural tumours, regardless of other tumour site(s)
<b>Stage IV</b>	any of the above with initial central nervous system and/or bone marrow involvement

#### ISCL/EORTC (*Mycosis fungoides and Sezary syndrome*)

This staging system assesses the tumour burden through four parameters: T (skin) N (node) M (viscera) B (blood).

	<b>T</b>	<b>N</b>	<b>M</b>	<b>B</b>
<b>I</b>	0	0	0,1	
<b>IB</b>	2	0	0	0,1
<b>II</b>	1,2	1,2	0	0,1
<b>IIB</b>	3	0-2	0	0,1
<b>III</b>	4	0-2	0	0,1
<b>IIIA</b>	4	0-2	0	0
<b>IIIB</b>	4	0-2	0	1
<b>IVA1</b>	1-4	0-2	0	2
<b>IVA2</b>	1-4	3	0	0-2
<b>IVB</b>	1-4	0-3	1	0-2

[Revisions to the staging and classification of mycosis fungoides and Sezary syndrome: a proposal of the International Society for Cutaneous Lymphomas \(ISCL\) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer \(EORTC\). Olsen E et al. ISCL/EORTC. Blood. 2007 Sep 15;110\(6\):1713-22. Epub 2007 May 31. Review. Erratum in: Blood. 2008 May 1;111\(9\):4830.](#)

#### VBSYMPTO Systemic symptoms

Systemic symptoms are: night sweats, weight loss (more than 10% of body weight in 6 months), fever > 38°C 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.

#### DISEASE INVOLVEMENT AT DIAGNOSIS

This information must be in the patients file.

#### MASSD Size of largest mass at diagnosis:

The label "No mass" indicates no bulky disease and it is possible to have "No mass" at diagnosis.

"Not measurable" indicates, for instance, BM infiltration which cannot be counted or measured in cm.

Some physicians record 'bulky disease' in the patient's notes and there are conflicting definitions as to what this means in terms of size so you need to check with your physician before completing this section. The information can be found in the description given by the radiologist (see CT- or MRT- scan or ultrasound).

#### LDHD LDH LEVELS

The LDH (lactate dehydrogenase) value refers to the level of this enzyme at diagnosis and can be found in the patients file. It is a prognostic maker with elevated values being unfavourable. The 'normal range' values vary between laboratories so it is important to check this on the lab form before assessing if the value is normal or elevated.

**Specific sites** at diagnosis: The information will be in the patients file. Please tick all organs/sites affected. If there is an organ or site affected that is not listed, please write it down under "Other".

## PRE-HSCT TREATMENT

### VPRETRAT TREATMENT PRE-HSCT

VCHEMOTH This means any treatment that is given for the disease before the transplant. If the transplant being reported is a second or higher transplant, it refers to treatment being given after the previous transplant and before the transplant being reported.

VRADIOTH Generally, first line therapy is given. If so, check **Yes** and give approximate **date** for start of treatment, and check appropriate box for modality/modalities. Blank boxes equate to missing data and will be queried. This information can be found in the patients file.

One 'line' of chemotherapy usually consists of repeated or alternating cycles of drugs according to a certain schedule. The term 'line' should not be confused with 'cycle' or 'course' of therapy: For example, initial treatment with four cycles of the VAD-regimen given every fourth week is one line of treatment, i.e. should be indicated under first line therapy, and NOT cycle 1 as first line therapy, cycle 2 as second line therapy etc. If there is no response to the first line of treatment, then an additional line of treatment is usually given.

If the indication for transplant is a transformed lymphoma, you should register the pre-HSCT treatment (and response/status) given since the transformation, rather than the original diagnosis.

OTHECHEM **Drugs given:** Please give the start date of the treatment prior to this HSCT and indicate all drugs given from that date until conditioning. A selection of drugs of current interest are listed on the MED-A form, but we would be grateful if you could list all drugs given. If any of the most common regimens (VAD, VBAP, VMCP, melphalan-prednisone = MP) has been used, just give the appropriate abbreviation. Otherwise, give the drug names. The treatment can include antibodies, radioactive antibodies, specific inhibitors, etc. If any of the inhibitors listed was given, please indicate whether the patient suffered disease relapse or progression during its use.

### TUMRSA2 RESPONSE TO THE LINE OF THERAPY

This information can be found in the patients file and is defined as follows:

**Complete remission (CR):** the patient has achieved complete absence of disease, there are no signs or symptoms of the original disease described.

**Partial remission/response (PR):** there was a reduction in the disease of 50% or more.

**No response:** Less than 50% reduction in disease.

### VPRETRAT ADDITIONAL PRE-TRANSPLANT TREATMENT

VCHEMOTH This information can be found in the patients file. A second line therapy is given if there was an unsatisfactory response to the first treatment, or if there was relapse or progression after a satisfactory response. It is also called *salvage therapy*. The same explanations apply as for FIRST LINE THERAPY.

## HSCT DATE

### IDAABC/IDAABE DATE OF HSCT

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.

## STATUS OF TREATMENT AND DISEASE AT HSCT

### MARKERS PRESENT AT ANY TIME BEFORE THE HSCT

Chromosomal alterations are associated with different types of lymphoma and are being shown to have a prognostic value for certain types of lymphoma, particularly B-cell NHL. This is also true for the expressed phenotype of the disease. For this reason, cytogenetics, molecular markers and/or immunophenotyping are requested for selected lymphomas at any time before the transplant. We give an example below on how to report the absence or presence of a chromosomal abnormality, a molecular marker or a certain phenotype:

Period	Abnormality status							
At diagnosis	No	Yes	No	No	Yes	Yes	No	Yes
At 1 <sup>st</sup> line treatment	No	No	Yes	No	Yes	No	Yes	Yes
At HSCT	No	No	No	Yes	No	Yes	Yes	Yes
Presence at any time before HSCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes

### VCHROMOS CYTOGENETICS

Indicate the absence or presence of the listed chromosomal abnormalities for the specified lymphomas. In the case of **del 17p**, indicate whether FISH was used to assess its presence.

To complete this item you should confer with the cytogenetics laboratory or your physician. If it is not possible, please send a copy of the results.

### VCHROMOS IMMUNOPHENOTYPING

Indicate the absence or presence of the listed phenotypes for the specified lymphomas.

### VCHROMOS MOLECULAR MARKERS

Indicate the absence or presence of the listed molecular markers for the specified lymphomas.

### TOTNTHET TREATMENT HISTORY

This information can be found in the patients file. Indicate here the total number of lines of therapy including those reported above.

### VCHEMOTA Modality used at least once

VIMMUNTA Fill in all modalities which have been used at least once in any treatment prior to the transplant.  
VRADIOTA

### VCRPRETR COMPLETE REMISSION AND RELAPSE HISTORY BEFORE THIS TRANSPLANT

CR achieved: ☐ Yes, date of first CR : .....

For definition of CR, PR and no response see above. It is vital the date is recorded. This can be found in the patients file.

If CR before transplant has never been achieved, mark "No".

### REFRPAST Was the patient refractory to a previous line of chemotherapy?

Indicate if the patient did not respond to at least one line of chemotherapy given prior to this HSCT.

### NBRCRBG Number of Complete remissions

Indicate the total number of CR's, including unconfirmed CRs, that the patient achieved before this transplant. Count the current CR if applicable. When reporting a subsequent HSCT, the Number of CRs should include all of

the CRs in the patient history (since Diagnosis date for the Lymphoma. If the transplant was given for a transformed lymphoma, count the number of CRs since the transformation).

#### NCRCRUPR Number of Partial remissions

Indicate the total number of PR's the patient achieved before this transplant. Count the current PR if applicable. When reporting a subsequent HSCT, the Number of PRs should include all of the PRs in the patient (since Diagnosis date for the Lymphoma. If the transplant was given for a transformed lymphoma, count the number of PRs since the transformation).

#### V1STRELA 1<sup>st</sup> 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 CR 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 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.

#### VSPLECNH HAS THIS PATIENT HAD A SPLENECTOMY?

Splenectomy means the removal of the spleen via a diagnostic laparotomy to examine if the spleen is affected or not. Most study groups do not recommend the splenectomy anymore because of the high risk of morbidity, potential lethality and absence of a survival advantage. But it may be useful for patients who shall get only radiotherapy.

## DISEASE STATUS AT HSCT

#### VCTSCAND CT scan done

Indicate if a CT scan was done to assess the patient disease status.

[Revised response criteria for malignant lymphoma](#). Cheson BD et al. J Clin Oncol. 2007 Feb 10;25(5):579-86. Epub 2007 Jan 22.

#### VPETSTAT PET results

Indicate the results obtained after PET. If PET was not used, answer "Not evaluated". This is very important to understand the accuracy of the assessment.

[Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification](#). Cheson BD et al. J Clin Oncol. 2014 Sep 20;32(27):3059-68.

#### Disease status VDISESTA

- |  |  |
|--|--|
| <input type="checkbox"/> Complete remission (CR)   | <input type="checkbox"/> Confirmed <b>VCRCONFI</b>   |
|  | <input type="checkbox"/> Unconfirmed CR  |
| CR confirmed   | there are no abnormalities detected in the scan. However, if there is previous history of a positive PET scan, a negative PET can be taken as confirmation of <b>Complete remission</b> 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); only applicable if assessed by CT scan (CRu does not apply to response assessed by PET)                                    |
| <input type="checkbox"/> Never treated   | The patient has never been treated for this disease  |
| <input type="checkbox"/> Partial response  | A reduction in disease of >50% compared to the pre-treatment burden  |
| <input type="checkbox"/> Stable disease  | A reduction in disease of <50% compared to the pre-treatment burden  |
| <input type="checkbox"/> Untreated relapse (from a previous CR) or untreated progression from a previous PR or progression | No further treatment has been given from the date of relapse or the date of progression  |

☐ Chemo refractory relapse or progression

The patient has not responded or has progressed during the treatment, including primary refractory disease

BM biopsy is not mandatory at this stage. If the indication for transplant is a transformed lymphoma, you should register the disease status of the transformed disease, not that of the prior diagnosis.

#### VINVOLVM **DISEASE INVOLVEMENT AT TRANSPLANT**

See disease involvement at diagnosis (above) for explanations. Patients in CR cannot have organ involvement.

## RESPONSE OF DISEASE AFTER HSCT

#### TUMRSA2 **BEST RESPONSE AT 100 DAYS AFTER TRANSPLANTATION**

Take the information from an examination performed around 100 days after transplantation. See definitions above. The information should be in the patient's notes.

**CRCONF11** You may find that if the patient has achieved complete remission after transplant, this CR may be described as confirmed or unconfirmed (see above). Please indicate this on the form.

If the situation is that the patient has achieved a complete remission but has a residual mass (CRu) we can say two things, complete remission unconfirmed or complete remission (if a PET scan has been performed and the PET is negative). In fact, most of the unconfirmed CR will simply be CR in the future if a PET is performed and it is negative.

You can use the same box, CR both for CR maintained or for CR achieved (see below). If CR was achieved, please indicate the date it was first seen. For baseline refer to "STATUS AT TRANSPLANT"

*The response date is the date that the sample or image was taken for assessing the response*

**CR maintained:** the status of disease at transplant was CR, and the status of the disease within 100 days post transplant is still CR.

**CR achieved:** the status of disease at transplantation was not CR, but the status of the disease after transplant is CR.

**DATRESP** If the patient achieved CR, indicate the date of CR.

If the patient died before 100 days after transplant, without being re-staged, please tick early death.

#### **Med-A only**

##### **Current disease status**

You must tick only one box. Indicate if the patient is in complete remission or not.

##### **Date achieved**

If the patient is in CR, enter the date it was achieved or assessed.

##### **Date assessed**

If the patient is not in CR enter the last date the patient's disease status was recorded.

## FORMS TO BE FILLED IN

#### **TYPE OF HSCT**

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic      the patient receives stem cells from another person  
Autologous    the patient receives his/her own stem cells back

Other      Please see page 13 **TYPE OF HSCT**

## FOLLOW UP

## LYMPHOMA

**VRELP** **PROG** **RELAPSE OR PROGRESSION AFTER TRANSPLANT**

For the definition on relapse please refer to 1st relapse in the pre-transplant section.

**Organs involved at relapse or progression**

The information will be in the patients file. Please tick all organs/sites affected. If there is an organ or site affected that is not listed, please write it down under “Other”.

All other items asked in the follow-up have been defined above or in the **General follow up** chapter of this manual.

SPECIFICATIONS  
OF THE DISEASE

# MYELODYSPLASTIC SYNDROME (MDS) OR MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASM (MDS/MPN) OR THERAPY RELATED NEOPLASM DIAGNOSIS

Myelodysplastic syndrome (MDS) is a heterogeneous group of clonal haematopoietic stem cell disorders characterised by an ineffective, dysplastic haematopoiesis, peripheral cytopenia and a variable rate of progression to AML. It is considered a pre-leukaemia.

It is a disease that can progress through different phases (subclassification) from the time of diagnosis to transplantation. One of these phases can be an acute myelogenous leukaemia (AML), and this often confuses data managers when trying to choose the correct form to complete. We offer below some explanations on how to deal with a diagnosis of AML. The other MDS phases will be described in more detail further down.

1) If the patient is transplanted for AML, even if they had a proven history of at least two months of MDS, they should be registered with AML as the primary diagnosis. (If there was a previous diagnosis of MDS or MDS/MPN, fill in the MDS or MDS/MPN MED-B form until *Status at HSCT*, then go back to the AML form and continue from *Predisposing Condition*). If you are using Promise, it will switch automatically during data entry.

2) An AML with prior exposure to chemo- or radiotherapy is considered a Therapy related neoplasm (old “Secondary Acute Leukaemia”) and the correct subclassification is gathered on the AML form, so you should register it with AML as the primary diagnosis. If you are completing MED-B, once you have registered the disease as AML, you are asked to submit the “MDS and Therapy related neoplasm” Med-B form instead of the “Acute Leukaemia” Med-B form. If you are using Promise, it will switch automatically during data entry.

## Other disease descriptions with their registration options:

- Fanconi Anaemia with/changing to MDS: This is a rare and very characteristic disease and it is important that it should be properly identified in the database. For this reason, please ensure when registering the MDS that the primary disease is clearly identified as Fanconi. If the patient had received treatment before the MDS developed, please register this treatment submitting the corresponding form: **Bone marrow failures Med-B Form**, which can be used to register treatment other than HSCT.
- -Aplastic Anaemia changing to MDS: it is possible that the patient has already been registered with an immunosuppression treatment or even a transplant as treatment for the AA. This should be checked to ensure that the patient is reported with the same patient identification codes. In all cases proceed as follows:
  - If the aplastic anaemia component of the patients history has not been reported, fill in the **Bone marrow failures Med-B Form** to report the diagnosis and treatment of the aplastic anaemia up to the date of transformation into MDS.
  - As soon as the patient progresses to MDS and a transplant is given for the treatment of MDS, the data subsequent to the diagnosis of MDS should be reported with the **Myelodysplastic Syndrome or MDS/MPN or Therapy related neoplasm Med-B Form**. Mark the subclassification as MDS at diagnosis indicating it is from secondary origin due to the immunosuppression (if given) or the haematological disease. Mark AA as primary disease with the date of diagnosis of the AA. This will help cross-checking to avoid double registrations of the same patient.
- Hypoplastic anaemia with MDS: These patients should be registered here, with the **Myelodysplastic Syndrome or MD/MPN or Therapy related neoplasm Med-B Form**. You should tick the subclassification as MDS at diagnosis, stage “Other” and write “hypoplastic anaemia” on the margin.

## MYELODYSPLASTIC SYNDROME VMDS

### (WHO)Subclassification

#### Peripheral blood and bone marrow findings in myelodysplastic syndromes (MDS)

Disease	Blood findings	Bone marrow findings
Refractory cytopenias with unilineage dysplasia (RCUD); Refractory anaemia (RA); Refractory neutropenia (RN); Refractory thrombocytopenia (RT)	Unicytopenia or bicytopenia <sup>1</sup> No or rare blasts (<1%)	Unilineage dysplasia: ≥10% of cells in one lineage <5 blasts <15% of erythroid precursors are ring sideroblasts
Refractory anaemia with ring sideroblasts (RARS)	Anaemia No blasts	≥15% erythroid precursors are ring sideroblasts Erythroid dysplasia only <5% blasts
MDS associated with isolated del(5q)	Anaemia Usually normal or increased platelet count No or rare blasts (<1%)	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts Isolated del(5q) cytogenetic abnormality No Auer rods
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s) No or rare blasts (<1%) <sup>2</sup> No Auer rods <1x10 <sup>9</sup> /L monocytes	Dysplasia in ≥10% of the cells in ≥ two myeloid lineages (neutrophil and/or erythroid precursors and/or megakaryocytes) <5% blasts in marrow No Auer rods ±15% ring sideroblasts
Refractory anaemia with excess blasts-1 (RAEB-1)	Cytopenia(s) <5% blasts <sup>2</sup> No Auer rods <1x10 <sup>9</sup> /L monocytes	Unilineage or multilineage dysplasia 5-9% blasts No Auer rods
Refractory anaemia with excess blasts-2 (RAEB-2)	Cytopenia(s) 5-19% blasts Auer rods ± <sup>3</sup> <1x10 <sup>9</sup> /L monocytes	
Myelodysplastic syndrome – unclassified (MDS-U)	Cytopenias ≤1% blasts	Unequivocal dysplasia in less than 10% of cells in one or more myeloid cell lines when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS <5% blasts

Bicytopenia may occasionally be observed. Cases with pancytopenia should be classified as MDS-U.

<sup>2</sup> If the marrow myeloblast percentage is <5% but there are 2-4% myeloblasts in the blood, the diagnostic classification is RAEB 1.

Cases of RCUD and RCMD with 1% myeloblasts in the blood should be classified as MDS, U.

<sup>3</sup> Cases with Auer rods and <5% myeloblasts in the blood and <10% in the marrow should be classified as RAEB 2.

In the past, MDS used to be classified according to the FAB (French-American-British)-classification which is a cytological (looks at cells) classification. This classification considers: percentage of blasts in peripheral blood and bone marrow, percentage of ring sideroblasts\* in the marrow, presence of Auer rods\*\* and number of monocytes in peripheral blood.

\*Sideroblasts are normoblasts with iron particles (iron staining: Perls).

\*\*Auer rods are rods in promyelocytes and myelocytes.

The FAB classification cannot be easily superimposed onto the WHO classification and it is for this reason, that both classifications are being requested.

#### (FAB)Subclassification

FAB-type	Description	Blasts in peripheral blood (%)		Blasts in bone marrow (%)		
RA	Refractory anaemia	< 1	and	< 5		
RARS	RA with ring sideroblasts	< 1	and	< 5	and	Ring sideroblasts > 15 %
RAEB	RA with excess of blasts	< 5	and	5 – 20		
RAEB-t	RAEB in transformation	> 5	or	21 – 30	or	Presence of Auer rods

#### MDSAMPS

#### ☐ MYELOYDYSPLASTIC / MYELOPROLIFERATIVE NEOPLASM

WHO	Description	Blasts in peripheral blood (%)		Blasts in bone marrow (%)		
CMML-1	Chronic myelomonocytic leukaemia	< 5	and	< 10	and	Monocytes > 1,000/mm <sup>3</sup>
CMML-2	Chronic myelomonocytic leukaemia	5%-19%	and	10 to 19%	and	Monocytes > 1,000/mm <sup>3</sup>
JMML	Juvenile myelomonocytic leukaemia	<5	and	< 20	and	Monocytes > 1,000/mm <sup>3</sup>

#### Chronic Myelomonocytic Leukaemia (CMML, CMML)

The WHO definition of CMML is more precise. Two types of CMML can be distinguished: dysplastic (WBC less than 13.000 mm<sup>3</sup>) and proliferative (WBC > 13.000 mm<sup>3</sup>). Patients with proliferative type have more splenomegaly, but regarding transformation into acute leukaemia and survival, no difference exist between both types. In fact, dysplastic CMML may evolve to proliferative CMML.

According to WHO, CMML can be further classified according to the number of blasts in peripheral blood and bone marrow into CMML-1 and CMML-2 (see table).

#### Juvenile Myelomonocytic Leukaemia (jCMML, jMML, jCML, jCMML)

A disease entity separate from the standard adults forms. The juvenile forms also include the juvenile monosomy 7 syndrome. Absence of bcr-abl rearrangement (t(9;22)) is one of the requested criteria for diagnosis. In addition to the requested criteria at least three of the following criteria must be fulfilled: increased foetal haemoglobin (HbF), myeloid precursors in the blood, WBC > 10,000/mm<sup>3</sup>, clonal abnormality (monosomy 7), GM-CSF hypersensitivity in vitro.

**Simultaneous diagnosis of MDS&MPN:** Note that in addition to the authentic combined MDS/MPN, a patient may be diagnosed with MDS and with MPN simultaneously. For these cases, please contact the EBMT Registry so that we can code it as a simultaneous diagnosis in the Registry database. Please state which of the diagnoses the transplant was given for as main diagnosis. (It could be one main indication only, or both)

#### VSECORIG

#### SECONDARY ORIGIN

The main options are the following:

#### DISSECD

#### -Chemotherapy / Radiotherapy treated disease

The syndrome has been preceded by chemotherapy or radiotherapy as treatment for a prior disease. The primary disease for which chemo- and/or radiotherapy were given should be mentioned at the topic "Primary disease". Indicate also the type of agent involved in the prior treatment.

-Immune suppression

Like -for instance- treatment with cyclosporin A or Imuran (azathioprine).

-After HSCT

This means that the prior disease was treated with a high-dose chemotherapy followed by stem cell transplantation

**DISMCLFD** **Primary disease + Date of diagnosis (*primary disease*) :**  
The “primary disease” is defined as the disease prior to the MDS/AL diagnosis if the answer to ‘secondary origin’ was “yes”.

**RPDRGRAD** MDS may also develop in donor cells when the patient has had a previous allograft. Please, indicate if this is the case for patient that fulfill this condition.

## CYTOGENETICS DATA

(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

If more than one analysis has been done since diagnosis but before treatment, indicate Abnormal if at least one analysis has been found to be abnormal. In this case, describe the results of the most recent analysis with abnormal results.

**VCHROMOS** **Chromosome analysis**  
See cytogenetics form or ask cytogenetics team *AND* consult your physician.

If abnormal: Are there 3 or more abnormalities (*complex karyotype*)?  
This concept allows to easily distinguish complex karyotypes from other abnormalities.

**CHRMABND** **Abnormalities** *Write chromosomes involved*  
Please fill in all abnormalities that were found. Common abnormalities in MDS are for instance; abnormalities on chromosome 5 and 7 and trisomy 8..

**MOLEBIO** **MOLECULAR BIOLOGY**  
For MDS/MPN, If markers are present, indicate clearly which have been found. It is important to identify each marker separately, indicating whether they have been evaluated or not.

The role that molecular markers may play in MDS prognosis is still not clear. It is important however to know that the analysis was done and whether markers were present or absent.  
If molecular biology analyses are done and no markers are found, please tick Absent.

---

## HAEMATOLOGICAL VALUES (*at diagnosis*)

**Peripheral blood**  
Make sure the values describe here are those used for the diagnosis.

**HBD**  
**Etc** Hb (the conversion factor for Hb in mmol/L to g/dL is 1.61), Platelets and White Blood Cells should be reported in absolute values, while blasts, monocytes and neutrophils should be reported as percentages.

### Bone Marrow

**PBLBMD** % blasts  
**VAUERD** Auer rods present

**International Prognostic Scoring system (IPSS) score** (Fill only for MDS and CMML; do not fill for Therapy related neoplasm, or JMML)

The IPSS risk score is a model which predict outcome of the patients according to cytogenetics, blasts in bone marrow and number of cytopenias, and distinguishes 4 risk categories: low, intermediate 1, intermediate 2 and high risk.

**Risk-Score acc. to the International MDS Workshop (IPSS)****Single factors**

Prognostic factors	Score				
	0	0,5	1,0	1,5	2,0
Count of blasts in the bone marrow	< 5 %	5 – 10 %	5 – 10 %	11 – 20 %	21 – 30 %
Karyotype*	low risk	intermediate risk	high risk		
Involved cell lines**	0 – 1	2 – 3			

\* Low risk: Normal karyotype, -Y, 5q-, 20q-.

High risk: Complex Karyotype, anomalies of Chromosome 7.

Intermediate risk: All other aberrations.

\*\* Count of involved cell lines (granulocytopoiesis, erythrocytopoiesis, thrombocytopoiesis). Hb should be less than 10g/dL, platelets less than  $100 \times 10^9/L$  and neutrophils less than  $1.5 \times 10^9/L$

**Risk groups**

Risk group	Score Sum	Risk of malignant transformation*	Median time of survival
Low risk	0	> 18	65 months
Intermediate 1 (Int 1)	0,5 – 1,0	8 years	40 months
Intermediate 2 (Int 2)	1,5 – 2,0	3 years	14 months
High risk	> 2,5	0,5 years	5 months

\* Time until development of AML (median).

**BMD****BM INVESTIGATION** (at diagnosis of MDS or the Therapy related neoplasm)

Indicate which technique has been used for the bone marrow investigation:

Cytology (the FAB classification is based on cytology only, not on histology)

Histology (cellularity and fibrosis are based on histology, not on cytology)

**RESULTS****VCCELLUL1****CELLULARITY**

The results are obtained from the marrow biopsy (histology).

Acellular: absence of cells ("dry tap")

Hypocellular: very little bone marrow cellularity.

Normocellular: normal situation.

Hypercellular: too much bone marrow cellularity.

Focal cellularity: hypocellular but locally cellular

Usually the examination of the BM aspirate is done by the haematologist. The result should be found in the haematology lab form.

**VFIBROS1****FIBROSIS**

If normal, that is with no fibrosis, tick "no". Otherwise, the level of fibrosis should be described in the pathology report since the examination of the biopsy (trephine) is done by the pathologist.

**FIRST LINE THERAPY**

**If this registration pertains to a second or subsequent HSCT the therapy number should be counted since last reported HSCT.**

If this patient had an Aplastic anaemia changing to MDS (see above), the information in this section pertains only to treatment given after the MDS has been diagnosed. The treatment for Aplastic anaemia should be reported with the Bone marrow failures Med-B Form, even if the patient did not have a transplant before the MDS was diagnosed.

The information in this section does NOT refer to the conditioning treatment.

IDAABC

Date started .....  
 yyyy mm dd

Indicate the first date of overall treatment.

### SUBCLASSIFICATION AT PRIMARY TREATMENT

From the time of diagnosis to transplantation these diseases can progress to more advanced stages, so please write down the stage at this point in time (*the subclassification of the disease just before the primary treatment for this disease*).

**VERY IMPORTANT:** The FAB-and the WHO classification of MDS cannot be “down-graded” after chemotherapy.

See SUBCLASSIFICATION AT HSCT for detailed explanations on how to provide this information.

### TREATMENT

The information in this item will be relevant for the indication of “status of disease at HSCT” (see below), so compatibility between these two items should always be ascertained.

Tick all the applicable treatments. Do not use **Other** to indicate blood transfusions.

VOTHERT

VCRPRETR **COMPLETE REMISSION** (*before HSCT*)

After remission induction therapy the patient may enter a complete remission (CR), which is defined by a marrow blast count below 5 % and a normalisation of peripheral blood counts for at least 4 weeks.

DATCR1 If so, please give the date (of the **first** CR.)

## SUBCLASSIFICATION & STATUS OF DISEASE AT HSCT

### DATE OF HSCT

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.

### Splenectomy

JMML ONLY: FILL IN SPLENECTOMY DETAILS

VSPLECN

### Splenectomy

Splenectomy means the removal of the spleen via a diagnostic laparotomy. If this has been done, please indicate the date.

### TRANSFUSIONS

Please record transfusion therapy for MDS since diagnosis

VMDSTRAN **SUBCLASSIFICATION AT HSCT**

The FAB-and the WHO classification of MDS cannot be “down-graded” after chemotherapy.

**Example 1:** once the diagnosis of RAEB-t is made, the patient disease subclassification will be at least a RAEB-t (could be upgraded to AL), even when there are no blasts in blood/bone marrow at the moment of transplant. The fact that there are no blasts means that this patient reacted to the chemotherapy and that he/she will be transplanted in CR, not that his MDS subclassification changed to RA.

**Example 2:** If a patient with RAEB *after chemotherapy* has 6% blasts in peripheral blood and 21% blasts in bone marrow he/she should be classified as RAEB-t (according to the FAB classification) at the moment of transplant. The disease did not react to the chemotherapy, but even progressed. This patient will be transplanted in primary refractory phase.

As was mentioned before; from the time of diagnosis to transplantation the stage of the disease can progress, so, please write down the *present* subclassification according to the staging of the disease at this point:

#### (WHO) Subclassification

- RA/RARS may develop into RAEB-1 and RAEB-2, R-CMD, RCMD-RS or sAML
- RCMD and RCMD-RS may develop into RAEB-1, RAEB-2 and sAML
- MDS with isolated del (5q) may develop into RAEB-1, RAEB-2 and sAML
- RAEB-1 and RAEB-2 may develop into sAML

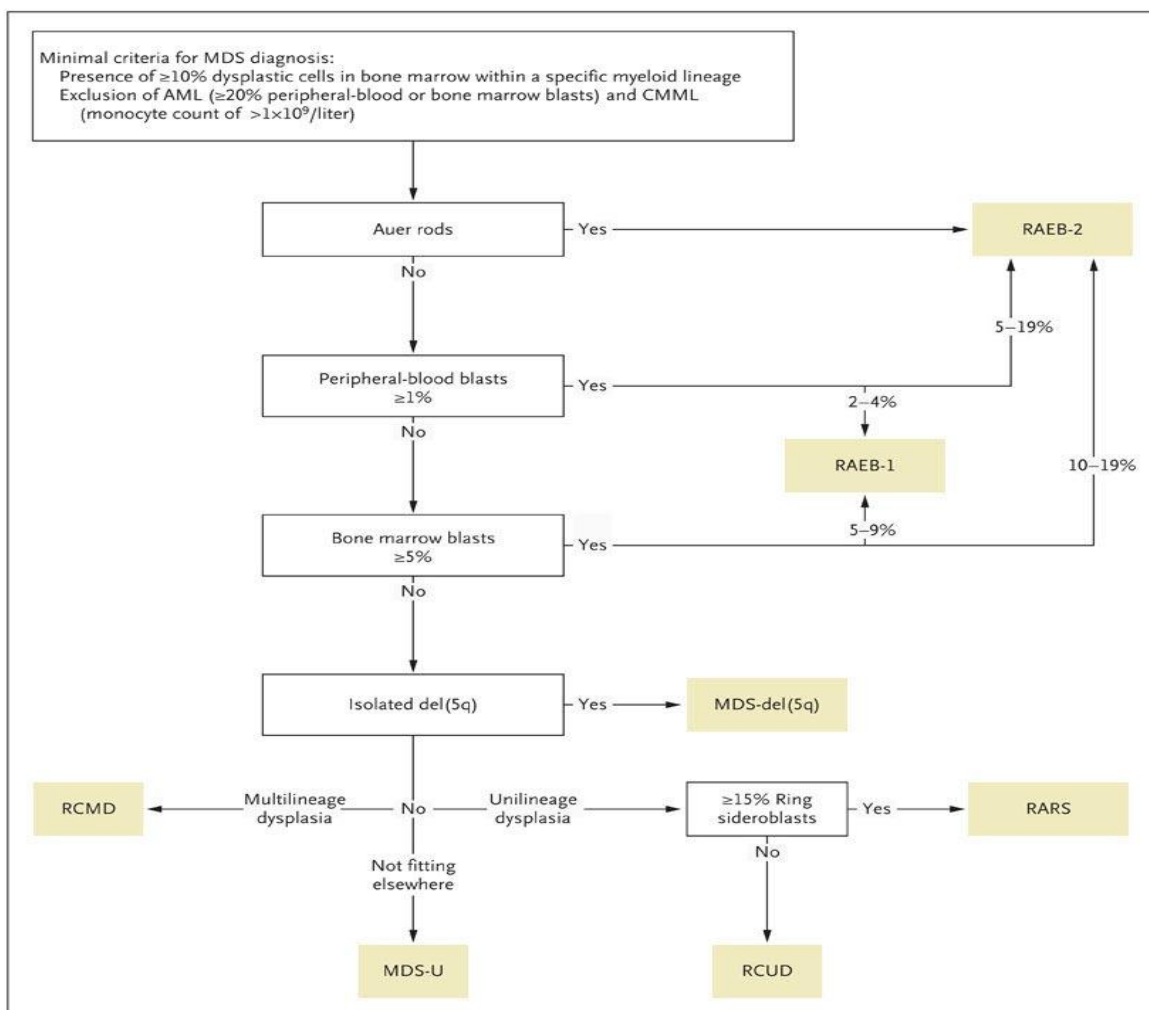
#### VMDS

#### (FAB) Subclassification

- RA and RARS may develop into RAEB, CMML, RAEB-t or s-AML
- RAEB may develop into CMML, RAEB-t or s-AML
- RAEB-t may develop into s-AML

Note: Please consider that sAML according to the FAB requires 30% blasts and according to the WHO only 20%!

The diagram below, taken from Tefferi, Vardiman NEJM 2009; 361: 1872-85 with permission, shows the possible paths of progression.



**VMDSMPS****Myelodysplastic and Myeloproliferative syndrome**

- CMML dysplastic type may develop into CMML proliferative type
- CMML1 may develop into CMML-2
- CMML1 and CMML-2 may develop into s-AML

**DISEASE STATUS AT HSCT**

Before filling in this part, please check the information you filled in under '**TREATMENT**', in the previous section, to ensure consistency. Disease status should not be reported for jMML.

**VDISESTA****-Primary refractory phase of disease**

Treatment with intent to achieve remission was given, but no remission was achieved

**-Complete remission (CR)**

Complete remission was achieved: marrow blast count below 5% and a normalisation of peripheral blood counts for at least 4 weeks

Indicate the number of this CR

**-Improvement but no CR**

Bone marrow blasts decreased by  $\geq 50\%$  over pretreatment but still  $> 5\%$

All CR criteria if abnormal before treatment

**-Relapse**

At least one complete remission was achieved with a previous treatment but the patient has relapsed since then.

Indicate the number of this relapse

**-Progression/worse**

More blasts in BM than before treatment

**-Never treated** (Supportive care or treatment without chemotherapy)

No treatment was given (blood transfusions are not considered treatment in this context)

**VCHROMOS****CYTOGENETICS** (*within 2 months before conditioning*)**HAEMATOLOGICAL VALUES** (*within one week before conditioning*)**IPSS SCORE****BM INVESTIGATION AND HAEMATOLOGICAL VALUES** (*within 2 months before conditioning*)**HBD**

PLAT, etc

Please see the explanations regarding these topics 'at diagnosis'

## ADDITIONAL TREATMENT POST-HSCT

**ADDITIONAL DISEASE TREATMENT**

☐ No

☐ Yes: ☐ Planned (*planned before HSCT took place*)

☐ Not planned (*for relapse/progression or persistent disease*)

Please specify whether or not additional treatment was given.

Additional cell therapies are not reported here. In both MED-A and MED-B, cell infusions are included elsewhere in the forms. Second transplants should not be reported in Additional Disease Treatment either: please complete a new MED-A or MED-B for additional transplants.

## BEST DISEASE RESPONSE AT 100 DAYS POST-HSCT

**TUMRSA2** The response should be measured approximately at 100 days after transplant.  
See above, under “Status of disease at HSCT” for definitions.

### Med-A only

#### Current disease status

You must tick only one box. Indicate if the patient is in complete remission or not. For baseline refer to “STATUS AT TRANSPLANT”

*The response date is the date that the sample or image was taken for assessing the response*

#### Date achieved

If the patient is in CR, enter the date it was achieved or assessed.

#### Date assessed

If the patient is not in CR enter the last date the patient’s disease status was recorded.

## FORMS TO BE FILLED IN

### **VTRANTYP** TYPE OF HSCT

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

Other Please see page 13 **TYPE OF HSCT**

**MYELOYDYSPLASTIC SYNDROME (MDS) OR  
MYELOYDYSPLASTIC/MYELOPROLIFERATIVE  
NEOPLASM (MDS/MPN) OR  
THERAPY RELATED NEOPLASMS**

☐ Previously reported

☐ No

### Haematological Relapse:

## LAST DISEASE AND PATIENT STATUS

SPECIFICATIONS  
OF THE DISEASE**MYELOPROLIFERATIVE NEOPLASM  
(OLD MPS)****DIAGNOSIS**

Myeloproliferative neoplasm (*syndrome*) (used to be known as MPS) presents usually with a hypercellular bone marrow with marked fibrosis, (hepato-) -splenomegaly, usually increased cell counts in the blood (anaemia is possible) and often a leuko-erythroblastosis, immature forms of red cells and white cells in the blood. With advanced disease the cellularity may be low and fibrosis becomes predominant, blood counts may be low and the patient may be transfusion dependent.

## VMPS

**SUBCLASSIFICATION**☐ **Myeloproliferative Neoplasm (*syndrome*)**

Chronic idiopathic myelofibrosis or **Primary Myelofibrosis**

proliferation of megakaryocytes which results in secondary fibrosis

**Polycythaemia Vera**

proliferation of erythrocytes (and leukocytes)

**Essential Thrombocythemia:**

proliferation of thrombocytes

**Hyper eosinophilic syndrome (HES)**

The patient is diagnosed with all of the following:

1. eosinophilia  $>1.5 \times 10^9/L$  for more than 6 months before transplant or transplant before 6 months associated with sign and symptoms of HES;
2. no evidence before transplant for parasitic, allergic, or other known causes of eosinophilia.
3. presumptive signs and symptoms of organ involvement.

**Chronic eosinophilic leukaemia (CEL)**

The patient is diagnosed with the following before transplant:

1. all the above criteria for HES are met
2. presence of a clonal chromosomal abnormality or at least 2 of the following:
  - $>25\%$  immature eosinophil precursors in PB or BM,
  - $>5\%$  myeloblasts in PB or BM,
  - eosinophils demonstrating positivity for naphtol chloroacetate esterase.

**With blastic transformation?**

The patient is diagnosed with all of the following before transplant:

1. the above criteria for CEL are met
2.  $>20\%$  myeloblasts in PB or BM.

**Stem cell leukaemia-Lymphoma syndrome (8p11 syndrome)**

Rare chronic myeloproliferative neoplasms that frequently present with eosinophilia and associated T-cell lymphoblastic lymphoma. This disease is aggressive and rapidly transforms to acute leukaemia.

**Systemic Mastocytosis**

**Myelofibrosis transformed from PV/ET**

Very rare. If the myelofibrosis is an evolution of **Polycythaemia Vera** or **Essential Thrombocythaemia**, please tick Myelofibrosis transformed from Polycythaemia vera/ Essential thrombocythaemia

Other disease descriptions with their registration options:

- Myelofibrosis with myeloid metaplasia should be registered as myelofibrosis
- Acute Myelofibrosis does not belong here; it should be classified as AML7, acute megakaryoblastic leukaemia (use **Primary Acute Leukaemia Med-B Form**)

**CYTOGENETICS DATA**(INCLUDE ALL ANALYSIS BEFORE TREATMENT; DESCRIBE RESULTS OF MOST RECENT COMPLETE ANALYSIS)

If more than one analysis has been done since diagnosis but before treatment, indicate abnormal if at least one analysis has been found to be abnormal. In this case, describe the results of the most recent analysis with abnormal results.

**VCHROMOS****Chromosome analysis**

See cytogenetics form or ask cytogenetics team *AND* consult your physician.

If abnormal: Are there 3 or more abnormalities (*complex karyotype*)?

This concept allows to easily distinguish complex karyotypes from other abnormalities.

**CHRMABND****Abnormalities** *Write chromosomes involved*

Please fill in all abnormalities that were found. Common abnormalities in MPS

are for instance: del 20q, trisomy 8, del 13q, trisomy 9 or abnormalities on chromosome 5

**MOLECULAR BIOLOGY**

Molecular markers :Myeloproliferative neoplasms have specific mutations: To distinguish these forms from CML, all forms should be bcr-abl negative. More than 90% of PV patients and about 50% of primary myelofibrosis and ET patients carry the JAK2 mutation. FIP1L1-PDGFR mutation can be found in HES, whereas c-kit mutation is found in systemic mastocytosis

**HAEMATOLOGICAL VALUES** (*at diagnosis*)**Peripheral blood**

Make sure the values describe here are those used for the diagnosis.

**HBD****Etc**

Hb, Platelets and White Blood Cells should be reported in absolute values, while blasts, monocytes and neutrophils should be reported as percentages.

**Bone Marrow****PBLBMD**

% blasts

**VAUERD**

Auer rods present

**RISK FACTOR SCORES****International Prognostic Scoring system (IPSS)** - *Primary myelofibrosis only*

The IPSS score identifies two distinctive prognostic groups depending on the number of adverse prognostic factors present:

Risk Group	No. of factors	Proportion of patients, %	Proportion of deaths, %
Low	0	22	32
Intermediate – 1	1	29	50
Intermediate – 2	2	28	71
High	>3	21	73

The risk factors are:

- Age > 65 y
- Constitutional symptoms
- Hb <10 g/dL
- WBC count > 25 x 10<sup>9</sup>/L
- Blood blasts > 1%

**BMD**

**BM INVESTIGATION** *(at diagnosis of MPS)*

Indicate which technique has been used for the bone marrow investigation:

Cytology

Histology (cellularity and fibrosis are based on histology, not on cytology)

**RESULTS****VCELLUL1 CELLULARITY**

The results are obtained from the marrow biopsy (histology).

Acellular: absence of cells ("dry tap")  
 Hypocellular: very little bone marrow cellularity.  
 Normocellular: normal situation.  
 Hypercellular: too much bone marrow cellularity.  
 Focal cellularity: hypocellular but locally cellular

Usually the examination of the BM aspirate is done by the haematologist. The result should be found in the haematology lab form.

**VFIBROS1 FIBROSIS**

If normal, that is with no fibrosis, tick "no". Otherwise, the level of fibrosis should be described in the pathology report since the examination of the biopsy (trephine) is done by the pathologist.

**CONSTITUTIONAL SYMPTOMS** *(at diagnosis)*

Constitutional symptoms are night sweat, fever without infection and weight loss.

**SPLMEGD**

Palpable Splenomegaly The spleen size is usually mentioned in the pretransplant summary or in the letter from the referring centre.

**VSPLEEND**

If only a physical examination has been done, please mention the centimetres below costal margin.

**VSPLCTSC**

If an ultrasound or CT scan has been done; please mention the largest diameter (in centimetres)  
 (In case of a discrepancy between the maximum diameters obtained by ultrasound **and** CT scan, report the maximum diameter obtained by ultrasound examination.)

## FIRST LINE THERAPY

***If this registration pertains to a second or subsequent transplant the therapy number should be counted since last reported transplant.***

The information in this section does NOT refer to the preparative (conditioning) treatment.

**SUBCLASSIFICATION AT PRIMARY TREATMENT**

From the time of diagnosis to transplantation this disease can progress to more advanced stages, so please write down the stage at this point in time *(the subclassification of the disease just before the primary treatment for this disease)*:

**VMPS****Myeloproliferative neoplasm (syndrome)**

- Any MPS subclassification may progress to acute leukaemia
- Polycythaemia vera and Essential Thrombocythaemia may progress to myelofibrosis ("secondary") and acute leukaemia

**TREATMENT**

The information in this item will be relevant for the indication of "status of disease at HSCT" (see below), so compatibility between these two items should always be ascertained.

The most frequent treatments for these group of diseases will be:

- Steroids
- Tyrosine kinase inhibitor (imatinib, danatinib, etc.)
- Hormones
- Thalidomide
- Lenalidomide
- Others

#### **VCRPRETR COMPLETE REMISSION** *(before BMT)*

After remission induction chemotherapy the patient may enter a complete remission (CR), which is minimally defined by a marrow blast count below 5 % and a normalisation of peripheral blood counts for at least 4 weeks.

For myelofibrosis, which is the most common indication for transplant, complete remission should be defined as follows:

1. Resolution of disease –related symptoms and signs including palpable hepatosplenomegaly.
2. Hb >11gr/dL, Platelet >100 x10<sup>9</sup>/L and neutrophils >1 x 10<sup>9</sup>/L.
3. normal bone marrow histology, and fibrosis grade no higher than 1

**DATCR1** If CR has been achieved, please give the date of the **first** CR.

## SUBCLASSIFICATION & STATUS OF DISEASE AT HSCT

### **DATE OF HSCT**

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.

### **Splenectomy**

Splenectomy means the removal of the spleen via a diagnostic laparotomy. If this has been done, please indicate the date.

### **Transfusional status at HSCT**

Indicate whether the patient has been receiving transfusions before the HSCT.

**VMDSTRAN SUBCLASSIFICATION AT HSCT****VMPS Myeloproliferative neoplasm (syndrome)**

- Any MPS subclassification may progress to acute leukaemia
- Polycythaemia vera and Essential Thrombocythaemia may progress to myelofibrosis ("secondary") and acute leukaemia

**RISK FACTOR SCORE****DIPSS Risk score** – Primary myelofibrosis only

The DIPSS risk score places a time-dependent risk evaluation over the original IPSS evaluation, generating a new prognostic score.

<i>Prognostic factors</i>	<i>Score</i>		
	<i>0</i>	<i>1</i>	<i>2</i>
Age	≤ 65	> 65	
WBC count (10 <sup>9</sup> /L)	≤ 25	> 25	
Hemoglobin (g/dL)	≥ 10		< 10
% Peripheral blood blasts	< 1	≥ 1	
Constitutional symptoms	No	Yes	

<i>Risk group</i>	<i>Sum of scores</i>	<i>Median OS (y)</i>
Low	<b>0</b>	Not reached
Intermediate-1 (Int 1)	<b>1 - 2</b>	14.2
Intermediate-2 (Int 2)	<b>3 - 4</b>	4
High	<b>5 - 6</b>	1.5

Passamonti *et al.* Blood, 2010; 115:1703-1708

**STATUS OF DISEASE AT HSCT**

Before filling in this part, please check the information you filled in under '**TREATMENT**', in the previous section, to ensure consistency.

**VDISESTA STATUS**

For myelofibrosis, which is the most common indication for transplant, disease status should be defined as follows:

If treated:

**-Complete remission (CR):**

The 3 following criteria must be true:

1. Resolution of disease –related symptoms and signs including palpable hepatosplenomegaly.
2. HB >11gr/dL, Platelet >100 x10<sup>9</sup>/L and neutrophils >1 x 10<sup>9</sup>/L.
3. normal bone marrow histology and fibrosis grade no higher than 1

**Clinical improvement(CI):**

Requires one criterion in absence of progression:

1. Haemoglobin increase of 2gr/dL or transfusion independence
2. Spleen reduction of 50%
3. 100% increase in platelet count and an absolute platelet count of at least 50 x 10<sup>9</sup>/L
4. 100% increase in ANC and an ANC of at least 0.5 x 10<sup>9</sup>/L

**-Relapse:**  
Loss of CR

**-Progressive Disease:**  
requires one of the following:

1. progressive splenomegaly
2. leukemic transformation
3. An increase of peripheral blood blast percentage of at least 20%

**-Primary refractory / no response**  
none of the above

**- Never treated (Supportive Care)**

No treatment was given (blood transfusions are not considered treatment in this context)

(If transformed to Acute Leukaemia at HSCT, report the status of the Acute Leukaemia).

**VHROMOS** **CHROMOSOME ANALYSIS, RISK FACTOR SCORE, BM INVESTIGATION, HAEMATOLOGICAL VALUES AND CONSTITUTIONAL SYMPTOMS** (at HSCT)  
**HBD** Please see the explanations regarding these topics 'at diagnosis'  
**PLAT, etc**

## ADDITIONAL TREATMENT POST-HSCT

### ADDITIONAL DISEASE TREATMENT

- ☐ No
- ☐ Yes: ☐ Planned (planned before HSCT took place)
- ☐ Not planned (for relapse/progression or persistent disease)

Please specify whether or not additional treatment was given.

*Additional cell therapies are not reported here. In MED-A it is stated: disease treatment apart from cell infusion. In MED-A and MED-B, cell infusions are already included elsewhere in the forms. Second transplants should not be reported in Additional Disease Treatment either: please complete a new MED-A or MED-B for additional transplants.*

## RESPONSE OF DISEASE

**TUMRSA2** **BEST RESPONSE AT 100 DAYS AFTER HSCT**

The response should be measured approximately at 100 days after transplant.  
See above, under "Status of disease at HSCT" for definitions.

**Med-A only**

**Current disease status**

You must tick only one box. Indicate if the patient is in complete remission or not. For baseline refer to "STATUS AT TRANSPLANT". The response date is the date that the sample or image was taken for assessing the response

**Date achieved**

If the patient is in CR, enter the date it was achieved or assessed.

**Date assessed**

If the patient is not in CR enter the last date the patient's disease status was recorded.

## FORMS TO BE FILLED IN

**VTRANTYP****TYPE OF HSCT**

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

Other Please see page 13 **TYPE OF HSCT**

# MYELOPROLIFERATIVE NEOPLASMS

☐ Previously reported

☐ No

☐ Continuous progression since last transplant

Loss of CR

requires one of the following:

1. progressive splenomegaly
2. leukemic transformation
3. An increase of peripheral blood blast percentage of at least 20%

## LAST DISEASE AND PATIENT STATUS

## DISEASE STATUS

**FIBROSIS/OSTEOSCLEROSIS ON BM BIOPSY**

## Myeloproliferative Neoplasms

SPECIFICATIONS  
OF THE DISEASEPLASMA CELL DISORDERS  
INCLUDING MULTIPLE MYELOMA

## INITIAL DIAGNOSIS

## VPLCEDS1 SUBCLASSIFICATION

This information is to be found in the patient's file. Aside from Multiple myeloma, the following diagnosis also form part of the Plasma cell disorder's group:

Plasma cell leukaemia

Solitary plasmacytoma

Multiple (*solitary*) plasmacytoma

Amyloidosis (NOTE: this diagnosis has a separate entry in this document)

POEMS

Monoclonal Gammopathy of Clinical Significance (MGCS)

Other plasma cell disorders, such as Nemanin myopathy, should be registered under "Other".

**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.

## VPLCEDS3

- **Common type** myeloma means the most usual form, with a complete monoclonal immunoglobulin (M-component) of usually IgG- or IgA-type, very rarely IgD or IgM 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.

## 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 (biclonal), may appear simultaneously in serum/plasma. For these cases, please note both types on the form and indicate which type has the highest value. The chain type of highest value will be entered in the database. Database users should still note the presence of the 2 chain types in the comments field.

## VPLCEDS4

**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.

**Plasma-cell leukaemia:** A rare entity, an aggressive 'in-between' of myeloma and acute leukaemia.

**Solitary plasmacytoma:** A solitary plasma cell tumour in bone, soft tissue or other organs, with no presence in the bone marrow. Sometimes a patient may have a plasmacytoma progressing to a generalised multiple myeloma. In this case please register the main diagnosis as multiple myeloma. For information you can write the date of the plasmacytoma diagnosis on the form. If you are entering it in the database directly, we recommend that you register a myeloma as normal, then go back and create a diagnosis record manually for the plasmacytoma (labelled as "other – non graft diagnosis"). For further details please see "Creating New Records Manually" in the Promise user guide, or contact the [Helpdesk](#).

**Primary Amyloidosis:** A separate MED-B form for primary amyloidosis is available. Please see definitions on page 24.

**Monoclonal Gammopathy of Clinical Significance (MGCS):** Unlike AL amyloidosis, most researches consider the heavy chain as the driving force of pathogenesis in MGCS. Myeloma criteria should be used here, so please refer further below, at the Response section.

NOTE that **MGUS** (Monoclonal Gammopathy of *Undetermined* Significance) is recorded under PCD/Other, as it has no code of its own in the database (unlike MGCS, which has)

**Other:** Rarely, plasmacytomas can occur on different sites simultaneously. This would be called “multiple solitary plasmacytoma”. It should be excluded that bone marrow infiltration exists. If bone marrow infiltration exists in combination with multiple plasmacytoma lesions, it would be a Multiple myeloma with extramedullary manifestation.

Below is a table to help indicating registration of the diagnosis where multiple plasma cell disorders have been diagnosed in the patient history:

<b>Main diagnosis is Multiple Myeloma (MM) indication for transplant</b>	
<b>Plasmacytoma:</b>	
Precedes the MM diagnosis	The plasmacytoma is not considered indication for transplant and we do not require that it be registered
<b>POEMS:</b>	
Simultaneous to the MM diagnosis	This would be considered as POEMS, and POEMS should be registered as indication for transplant
After transplant for MM	POEMS, to be registered as secondary malignancy
<b>Monoclonal Light and heavy chain deposition disease (LCDD/HCDD):</b>	
Precedes the MM diagnosis	LCDD/HCDD is considered as a diagnosis on its own. However, if it is not considered to be indication for transplant, it does not need to be registered.
Simultaneous to the MM diagnosis	If LCDD/HCDD is considered to also be indication for transplant, then both diagnoses should be registered as main.
After transplant for MM	LCDD/HCDD, to be registered as secondary malignancy
<b>Amyloidosis:</b>	
Precedes the MM diagnosis	Both diagnoses to be registered independently and both considered to be indication for transplant
Simultaneous to the MM diagnosis	
After transplant for MM	Amyloidosis to be registered as a secondary diagnosis

#### VSALMDUR STAGE AT DIAGNOSIS (Salmon and Durie) and 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).

**VSALMDUR** Add 'A' or 'B' depending on renal function:

- **A** indicates normal or slightly impaired renal function with a serum-creatinine value of < 180 µmol/L,
- **B** indicates more severely impaired function with serum-creatinine = 180 µmol/L.

**ISS** **ISS** (International Staging System) is defined as shown in the table below:

<b>ISS</b>		
	$\beta 2$ µglob (mg/L)	Albumin (g/L)
<input type="checkbox"/> I	<3.5	≥35
<input type="checkbox"/> II	<3.5	<35
	3.5 – ≤5.5	-----
<input type="checkbox"/> III	>5.5	-----

## CYTOGENETICS AND MOLECULAR DATA

Retrieved from patients files.

**VCHROMOS** **Chromosome analysis:** Very important since specific abnormalities, particularly on chromosome 13 have emerged as one of the major prognostic factors. To be filled out as carefully as possible in each single patient. The most important information to be given here is whether chromosome analysis has been done successfully or not, whether it is normal or abnormal and, if abnormal, which chromosomes show abnormalities.

**VNUMETAN** Please indicate the number of metaphases examined and the number of metaphases with anomalies. These numbers are essential to determine the level of abnormality and accuracy of the measurement. The abnormalities listed are those most relevant in this setting. If the abnormality is not listed, please enter it under "Other .... (specify)"

**MOLEBIO** **Molecular analysis:** Indicates if bone marrow sampling at diagnosis or prior to treatment, for identification of a patient-specific disease-related DNA-sequence, has been done or not. Might be difficult to retrieve from patient files; if in doubt, ask the treating physician.

## CLINICAL AND LABORATORY DATA

**HBD**  
**UMIGD**  
**SMIGD**  
 etc  
**PPLABMD** Found in the laboratory printouts in the patient's files. Indicate the values from a date close to the date of diagnosis. The most important values are those for **Monoclonal Ig in serum, monoclonal Ig in urine, and serum beta-2 microglobulin.**

**BM aspirate, % plasmacytosis:** Indicates the percentage of plasma cells of the total number of nucleated cells in cytologic bone marrow smears.

**BM trephine, % plasmacytosis:** 'Trephine' means a special technique for bone marrow biopsy. Frequently not done in myeloma. A percentage value would be difficult to calculate from this type of biopsy, so this question is

poorly applicable. This question may be left unanswered on most occasions where a marrow aspirate is available which is generally the case. If doing so, please specify “not done”.

- SMIGD Monoclonal Ig in serum (g/L):** Very important information! A frequently used synonym for monoclonal IG is M-component. Applicable to ‘common’ myeloma, but not to light chain myeloma, since such patients have only polyclonal but not monoclonal Ig in serum. Be sure to give the value of the monoclonal Ig: For example, the total IgG in a patient might be 53 g/L, but of this only 48 g might be monoclonal and the remaining 5 g polyclonal; in this situation, the correct figure to indicate in the report is 48.
- UMIGD Monoclonal Ig in urine (g/24 hours):** Very important information! Synonyms: Urinary light chains (kappa or lambda chains) or Bence Jones’ protein. Applicable primarily to light chain type myeloma, although patients with ‘common’ myeloma sometimes also have a urinary excretion of light kappa or lambda chains. In any of these situations a value should be indicated if available.
- VSERBE2D Serum beta-2 microglobulin (mg/L):** Very important information, if available. Beta-2 microglobulin at diagnosis is one of the most important prognostic factors.
- XBONED INVOLVEMENT AT DIAGNOSIS**  
**Bone structure (X-ray):** Indicates the findings on conventional X-ray, not magnetic resonance tomography or CT scan. For **lytic lesions** it is very hard to give exact definitions of ‘minor’ and ‘major’ (e.g. several small lesions could still be minor, but only two large or dangerously localized lesions could be major), so this classification in each individual patient is to be determined by the treating physician; please ask if it is not clearly stated in the patient’s notes.
- VINVOLVM Extramedullary involvement:** Evidence of disease in other sites such as skin, liver, spleen, CNS etc.

## PRE-HSCT TREATMENT

- VPRETRAT WAS THE PATIENT TREATED BEFORE THE HSCT PROCEDURE**  
 One sequential treatment of chemotherapy usually consists of repeated cycles of the same type or different type of cycles repeated according to a certain schedule. The term ‘sequential number of treatment’ should not be confused with ‘cycle’ or ‘course’ of therapy: For example, initial treatment with four cycles of the VAD-regimen given every fourth week is one sequential number of treatment, i.e. should be indicated under first sequential number of treatment, and NOT cycle 1 as first sequential number of treatment, cycle 2 as second sequential number of treatment etc.
- On rare occasions, allogeneic transplantation or stem cell mobilisation followed by autologous transplantation is performed upfront without prior conventional pre-HSCT therapy. If this is the case, check the **No** box and proceed directly to Date of HSCT and type, then to **Disease Status at HSCT** for allogeneic transplantation or to **Status of disease at Collection** for autologous transplantation, and on the respective of these latter parts, check the box **At diagnosis** and continue (see below).
- VCHEMOTH Chemotherapy regimen:** If any of the most common regimens (VAD, VBAP, VMCP, melphalan-prednisone = MP) has been used, just give the appropriate abbreviation. Otherwise, give the drug names.

**TURMSA2**

## RESPONSE

Very important! Please, always fill this part.

All response categories require two consecutive assessments made at any time before the institution of therapy and are measured against pre-treatment values [Durie et al. **Leukaemia** (2006) 20: 1467-1473].

**sCR (stringent complete remission)-** All of the following:

- CR as defined below
- normal free light (FLC) 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 and 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
- Disappearance of any soft tissue plasmacytomas.
- No increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory)

If any investigation above has not been done, and all others are indicative of a CR, the status should be registered as VGPR.

Where CR has already been attained (bone marrow evaluation included) it may not be necessary to do a bone marrow evaluation again to confirm that the patient is still in CR (all other criteria confirming CR).

Therefore, the patient is still in CR.

**VGPR (very good partial remission)-** One or more of the following:

- Serum and urine M-protein detectable by immunofixation but not on electrophoresis
- $\geq 90\%$  reduction in serum M-protein plus urine M-protein level  $< 0.1\text{g/ per 24h}$

In addition, there must be no increase in size or number of lytic lesions if assessed (radiographic studies are not mandatory)

If any investigation above has not been done, and all others are indicative of a VGPR, the status should be registered as PR.

**PR (partial remission)-** All of the following:

- $\geq 50\%$  reduction in serum M-protein plus reduction in 24h urinary M-protein by  $\geq 90\%$  or to  $< 0.2\text{g/ per 24h}$   
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:
    - $\geq 50\%$  reduction in plasma cells provided baseline bone marrow plasma cell percentage was  $\geq 30\%$
- A reduction of more than 50% in the size of soft tissue plasmacytomas if present at pre-treatment.
- 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 and urine (absolute increase must be  $\geq 0.5\text{g/dL}$ ). (*Not applicable to light chain myelomas*).
- Increase of 25% or more in urinary light chains (absolute increase must be  $\geq 0.2\text{g/ per 24h}$ )  
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  $> 0.01\text{g/dL}$  from nadir)
- An increase of 25% or more in bone marrow plasma cells (absolute % must be  $\geq 10\%$ )
- Increase of old/appearance of new osteolytic bone lesions on x-ray
- Appearance of soft tissue plasmacytoma
- Development of hypercalcemia (corrected serum calcium  $> 11.5\text{ mg/dL}$  or  $2.65\text{ mmol/L}$ ) that can be attributed solely to the plasma cell disorder

**TYPE OF HSCT**

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

Other Please see page 13 **TYPE OF HSCT**

## STATUS OF DISEASE AT COLLECTION (AUTOGRAFTS ONLY)

Indicates the situation immediately prior to chemotherapy and/or hematopoietic growth factor treatment for mobilisation of hematopoietic peripheral blood stem cells to be used for autologous transplantation. The timing of this procedure should be evident from the notes in the patient file. For the laboratory values pick a date or dates as close as possible before the initiation of this treatment.

This is a very important item and should always be filled!

The definitions of **Complete remission**, **Partial remission** and **Progression** can be found under **Response** above in this manual. Other possible disease status are defined as follows:

**Relapse from CR:** Similar to progression but the reference point is a **Complete remission**.

One or more of the following:

- Reappearance of measurable monoclonal immunoglobulin in serum and 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

For **Complete remission**, **Partial remission** and **Relapse (from CR)** indicate the number of the status.

- **CR2** indicates that the patient has been in first CR after first or second pre-HSCT treatment, then relapsed and eventually was put in a second CR by second/third pre-HSCT treatment, respectively, which means that if CR2 is checked, CR must also be the last treatment response checked at second or third pre-HSCT treatment for everything to be coherent.
- The same is applicable to **>CR2**, which would however be a very rare situation.
- **PR2** indicates that the patient has been in PR after first or second pre-HSCT treatment, then progressed, and eventually responded again with a second PR by second/third pre-HSCT treatment, which means that if PR2 is checked, PR must also be the last treatment response checked at second or third sequential number of treatment for everything to be coherent. If there has been a CR at any point before the PR, indicate status as only PR without a number.
- The same is applicable to **>PR2**. If there has been a CR at any point before the PR, indicate status as only PR without a number.

**PLATEAU**

**Plateau** is applicable in patients in Stable disease or PR, and is defined as a plateau level in the serum monoclonal immunoglobulin or urinary light chains, i.e. that these values are unchanged in 2 separate samples at least 4 weeks apart. A plateau is frequently not awaited in patients planned for a transplantation, e.g. the patient is treated with a fixed number of pre-HSCT treatments until the monoclonal immunoglobulin/urinary light chain value fulfils the criterion for PR in one single value (the lowest value available), and the patient then proceeds directly to the next treatment step, i.e. stem cell mobilisation. In this frequent case, check the box '**Unknown**' for plateau.

This question is not applicable for '**Non-secretory**' myeloma.

**CLINICAL AND LABORATORY DATA**

See same section under diagnosis.

**VSERIMMF Immunofixation of serum / urine**

**VGMINF** For patients in CR, it is very important to indicate whether this CR was determined by the more sensitive method of **Immunofixation** of serum or urine, or by the older, less sensitive, standard electrophoresis method. If CR has been determined by immunofixation, check '**Negative**' in the appropriate slot for urine and / or serum. If CR has been determined by electrophoresis and immunofixation has not been performed, check '**Unknown**'.

If patient is not in CR, and immunofixation has been performed it will be '**Positive**'. Information on whether immunofixation has been done or not should be indicated on the appropriate laboratory report for protein analysis in the patient file. If still uncertain, ask the treating physician who should know whether immunofixation is done in the laboratory of the respective hospital.

## DISEASE STATUS AT HSCT

**VDISESTA** To be completed in all patients. For details, see previous section RESPONSE and STATUS OF DISEASE AT COLLECTION above.

## ADDITIONAL TREATMENT

**ADDPROT ADDITIONAL DISEASE TREATMENT**

Please specify whether or not additional treatment was given.

Planned means the specifications for the additional treatment had already been agreed prior to the HSCT and are not a reaction to disease assessment after the transplant.

For example, thalidomide is disease treatment in the case of a myeloma.

- If thalidomide is given as maintenance then it is "planned".
- If thalidomide is given for myeloma relapse then it is "not planned".

Biphosphonates and immunoglobulins are not considered as disease treatment, this is part of supportive care.

Additional cell therapies are not reported at this level in the Med-B form. These cell therapies are included elsewhere in the graft specific inserts.

Subsequent transplants should not be reported in Additional Disease Treatment either: please complete a new MED-A or MED-B for additional transplants.

## STATUS OF DISEASE AT 100 DAYS AFTER HSCT

**BEST RESPONSE TO HSCT AT 100 DAYS**

**TUMRSA2** For response definitions see previous RESPONSE section of this Myeloma manual. Response must be assessed prior to additional non-planned disease treatment.

For baseline refer to "STATUS AT TRANSPLANT"

*The response date is the date that the sample or image was taken for assessing the response*

**DATRESP** **Date of CR:** Very important. Give date if CR was reached at the time of the report.

In Multiple myeloma it is possible that the best response is not reached until more than 100 days have elapsed; in some rare cases it may even take more than year for a complete remission to establish itself. For this reason, this question should be revisited on the first and second yearly follow up after the transplant.

### Med-A only

**Never in CR** indicates the patient has never had a CR after the transplant, including a CR that does not comply with the requirements for it to be stringent (SCR). In order for CR to be selected, all tests need to be done and found to be negative.

**IMPORTANT** for *ANNUAL FOLLOW UP*: The definitions for Complete Remission (CR) in Myeloma follow rigorous criteria which require investigation that are not routinely done at follow up. Therefore, if the patient is considered to be in CR at the annual follow up, and there is no evidence of relapse or progression through the routine hospital assessments, that would be sufficient to record a CR. This is important because otherwise the patients end up being declared as in partial remission (PR), simply because one of the required investigations has not been done at the annual follow up stage.

## FORMS TO BE FILLED IN

### **VTRANTYP** **TYPE OF HSCT**

Check the type of transplant performed and proceed to the corresponding report form.

Allogeneic	the patient receives stem cells from another person
Autologous	the patient receives his/her own stem cells back

Other Please see page 13 **TYPE OF HSCT**

## FOLLOW UP

PLASMA CELL DISORDERS  
INCLUDING MULTIPLE MYELOMA**TUMRSA2** COMPLETE HAEMATOLOGICAL REMISSION OBTAINED AFTER THE HSCT IN THE ABSENCE OF  
ADDITIONAL DISEASE TREATMENT

**DATERESP** Very important! In this type of disease, complete remission may not be seen until after 100 days have relapsed since transplant. For this reason, the question is repeated in the follow up form. If CR, it is also very important to give the date. If the exact date cannot be retrieved, please make an approximation.

## LAST DISEASE AND PATIENT STATUS

For definitions see applicable parts of this Myeloma manual.

In Med-A, the question is posed differently:

**DISCLI** **Last disease status**  
Was disease detected by clinical/haematological method?:

The only options are Yes (patient not in CR) or No (patient in CR). Fill in the last date in which the disease was assessed.

PLEASE NOTE that in order to answer No to this question, you need to have **all** tests done and all of them be negative. In order to answer Yes, you need **at least one** of the tests to be positive. If not all tests are done, and those that are done are negative, then you answer Not Evaluated.

SPECIFICATIONS  
OF THE DISEASE

## SYSTEMIC SCLEROSIS

## DIAGNOSIS

Systemic sclerosis (SSc) is a heterogeneous condition of unknown etiology characterised by microvascular injury and the deposition of excess collagen in skin and internal organs. Systemic sclerosis is the prototype fibrosing disease. A genetic predisposition may be present, but genetic factors have been difficult to identify due to the low incidence and prevalence of the disease. For those affected, the prospect of significant morbidity and risk of early death contribute to the significant burden of the disease. Severe forms of the disease, and rapidly progressive diffuse SSc in particular, are associated with a significant mortality (estimated to be 40-50% in 5 years) secondary to cardiac, renal and, particularly, pulmonary involvement.

Two clinical patterns of lung involvement are recognized: precapillary vascular disease and interstitial lung disease (ILD), which has become the leading cause of death in SSc since the introduction of ACE-inhibitors to treat previously fatal renal crisis. Vasculopathy may lead to pulmonary arterial hypertension (PAH) even in the absence of significant fibrosis. PAH, defined as a mean pulmonary artery pressure higher than 25 mmHg at rest or higher than 30 mmHg during exercise in the absence of left-sided heart disease, occurs in at least 10% of SSc patients, and is associated with high mortality. Lung fibrosis has been found in approximately 70% of SSc patients at autopsy. Most studies differentiate scleroderma associated PAH and ILD as 2 separate pathological processes, concentrating on one or the other. Many patients though have both conditions. ILD is more frequent in dcSSc (53%) than in lcSSc (35%), whereas PAH is diagnosed in a similar frequency within the two subsets.

**MAIN DIAGNOSIS**

Skin thickening, Raynauds phenomenon are the key clinical features of systemic sclerosis. For scientific purposes, classification criteria have been set up by the American College of Rheumatology, referred to as **ACR criteria**.

*Criteria for the classification of systemic sclerosis (scleroderma)*

- 
1. Major criterion: Proximal scleroderma
  2. Minor criteria :
    - Sclerodactyly
    - Digital pitting scars or loss of substance of the digital finger pad
    - Bibasilar pulmonary fibrosis
- 

One major or two or more minor criteria are necessary to establish a diagnosis of SSc. A further subclassification can be made in limited (cutaneous) SSc (lSSc) and diffuse (cutaneous) SSc (dSSc).

*Limited SSc* is characterised by skin involvement limited to hands, feet, face and/or forearms, is associated with a high incidence of anticentromere autoantibodies (ACA) (70-80%), the existence for years of Raynaud's phenomenon and a significant late incidence of pulmonary hypertension. The acronym CREST (Calcinosis, Raynaud's phenomenon, Esophageal dysmotility, Sclerodactyly and Telangiectasia) fits into this subclassification.

*Diffuse SSc* is characterised by skin involvement on upper arms and trunk, is associated with an early incidence of interstitial lung disease, hypertensive crisis and renal failure, diffuse gastrointestinal disease and myocardial involvement, and the presence of anti-topoisomerase (or anti-Scl70) antibodies.

Both forms of the disease are associated with vascular abnormalities clinically manifest as Raynaud's phenomenon, and with antinuclear antibodies (ANA).

**LABORATORY VALUES**

Serum creatinine, creatinine clearance, and proteinuria are assessed as renal function can be impaired in SSc. Elevated creatine phosphokinase may point to inflammatory muscle involvement.

**AUTOANTIBODIES**

The presence of different types of antibodies are necessary for complete classification of the disease; see above.

## FIRST LINE THERAPIES

Until recently there existed no proven effective disease modifying therapy to prevent disease progression or reverse fibrosis. Clinical trials of D-Penicillamine, alpha-interferon, 5-fluorouracil and chlorambucil have been unable to demonstrate a clinically significant effect.

Methotrexate showed beneficial effects on skin thickening but not on organ dysfunction in a small placebo-controlled cross-over study and a large multicenter, prospective placebo-controlled, randomized trial.

Corticosteroids ((methyl)prednisolone, dexamethasone) are the cornerstone in the treatment of lung fibrosis associated with connective tissue diseases, but there is no evidence for their efficacy as monotherapy in SSc. Importantly, a retrospective case-control study showed that high-dose corticosteroid therapy, i.e. 15 mg/day prednisone or equivalent, is associated with the development of scleroderma renal crisis, which may lead to irreversible renal failure. Low doses of prednisone are effective, however, in the treatment of inflammatory muscle and/or joint involvement.

Of all immunosuppressive drugs, only cyclophosphamide with or without corticosteroids has been shown to improve skin thickening, stabilize pulmonary function and increase survival in a number of nonrandomized studies, particularly in early disease. Although studies were heterogeneous with respect to diagnoses, treatment protocols, and assessment criteria, the consistent effects on skin and lung function, notably in patients with diffuse skin disease and biochemical evidence of acute phase reactivity and/or active alveolitis, strongly suggest a disease-modifying effect. The beneficial effects intravenous and oral cyclophosphamide on lung involvement and skin have recently been confirmed in two prospective placebo-controlled multicenter clinical trials in the US and the UK. It is important to document whether the cumulative dose reflects intravenous versus oral treatment. Biologicals (infliximab, rituximab etc) are increasingly used in the treatment of rheumatic diseases, including SSc, although the evidence for their efficacy in the latter disease is anecdotal.

The effectiveness of cyclophosphamide on alveolitis and skin disease in SSc has prompted studies to investigate feasibility, safety and efficacy of dose-intensification of cyclophosphamide with or without additional lymphoablative agents, followed by autologous hemopoietic stem cell transplantation (HSCT) in severe SSc and other autoimmune diseases (J van Laar, D Farge, A Tyndall, *Ann Rheum Dis* 2008).

Ultraviolet-A1 phototherapy and extracorporeal photochemotherapy are frequently used by dermatologists to treat patients with fibrosing disorders, but compelling evidence of efficacy is lacking as illustrated by a recent randomized, double-blind, placebo-controlled trial of photopheresis in systemic sclerosis. One of the key problems in clinical trials in systemic sclerosis, is the spontaneous improvement of skin thickening in most patients.

## STATUS OF DISEASE AT MOBILISATION

## STATUS OF DISEASE AT HSCT

### DISEASE STATUS

There is no universally accepted disease activity score for SSc, which is why skin, and organ involvement are assessed separately.

The modified Rodnan skin score is a validated score to assess the extent of skin thickening with prognostic value: (persistently) high scores are associated with a worse outcome. Seventeen bodily areas (face, anterior chest, abdomen, upper arms, forearms, hands, fingers, thighs, lower legs, feet) are each scored for skin thickness on a scale from 0 to 3 (0=normal, 1=mild, 2=moderate, 3=severe), resulting in a maximum score of 51. The scoring requires training, and serial scores should be preferably done by one assessor to avoid interobserver variability.

### LABORATORY VALUES

**AUTOANTIBODIES**

See above, at Diagnosis.

**PHYSICAL EXAMINATION RESULTS**

Restrictive pulmonary function refers to a decreased (forced) vital capacity at lung function testing, arbitrarily set at less than 80% of predicted. It is usually caused by lung fibrosis. The mean PAP reflects pulmonary arterial pressure (see above), and can be noninvasively measured with echo, or more accurate through right heart catheterisation.

**INVOLVEMENT AND INDICATION FOR HSCT****Severe functional impairment**

Functional disability is a major health problem in patients with systemic sclerosis. In the setting of clinical trials, this is assessed using the health assessment questionnaire disability index (HAQ-DI), a validated scoring system, ranging from 0 to 3, with 0 representing normal function, and scores 1.5 and higher generally indicating severe disability.

## RESPONSE OF DISEASE

**Med-A only**

There are no accepted response criteria in systemic sclerosis, although some authors have made an attempt to do so. In general, most transplants in systemic sclerosis are done in the context of a clinical trial, and the CR and Never in CR responses should be defined as per that protocol.

**Current disease status**

You must tick only one box. Indicate if the patient is in complete remission or not. For baseline refer to "STATUS AT TRANSPLANT"

*The response date is the date that the sample or image was taken for assessing the response*

**Date achieved**

If the patient is in CR, enter the date it was achieved or assessed.

**Date assessed**

If the patient is not in CR enter the last date the patient's disease status was recorded.

## FOLLOW UP

## SYSTEMIC SCLEROSIS

Indicate the number of times the patient had a significant improvement followed by a significant worsening since. Number should be counted from last HSCT.

Number of relapses/progressions since last HSCT.....

☐ Unknown

SPECIFICATIONS  
OF THE DISEASE

## SYSTEMIC LUPUS ERYTHEMATOSUS

## DIAGNOSIS

Systemic Lupus Erythematosus (SLE), as defined according to the American College of Rheumatologists (ACR) criteria, is the most frequent systemic connective tissue disease with a prevalence of 40 to 50 / 100 000 people. Its exact origin is still unknown, but heredity, environment and hormonal changes may be involved. SLE is a heterogeneous chronic multisystemic autoimmune inflammatory disorder, with various types of clinical symptoms affecting mostly females (> 85%), with a higher frequency in certain ethnic groups, especially among black people.

**DIAGNOSTIC CRITERIA FOR SYSTEMIC LUPUS ERYTHEMATOSUS**

Several criteria are necessary to establish the diagnosis of SLE, with at least the presence of four diagnostic criteria, either simultaneously or successively in a single patient. Each criterion category corresponds to a type of disorder or organ manifestations with one or various symptoms as listed in the corresponding definitions. All these symptoms are indeed related to microvascular inflammatory lesions, due to the ongoing autoimmune process and activation, which may be in any vascularised part of the body. This contributes to various clinical manifestations which may account for one type of clinical criterion:

Skin manifestations are common in SLE, thus accounting for several categories of diagnostic criteria such as the presence of a malar rash (also called the “lupus mask” because it appears exclusively on the face), a discoid rash (which may appear in other places anywhere on the body surface), photosensitivity or oral ulcers (which have to be searched for by careful examination of the interior mouth).

Articular manifestations account as a single clinical diagnostic criterion, if arthritis is present with at least two joints involved with tenderness, swelling or effusion.

Serositis with 2 major localisations as defined by the presence of an inflammatory pleuritis (effusion in the pleura-around the lungs with classic and severe pleuritic chest pain OR rub OR effusion OR new pleural thickening) or pericarditis (effusion in the pericardium around the heart with classical and severe pericardial pain OR rub OR effusion OR EKG/ECG changes).

Renal dysfunction is one of the hallmarks of SLE and should be carefully evaluated in every patient not only by clinical symptoms used to assess renal function (24 hour urinary measure, presence of abnormal blood (red cells or haemoglobin) or white cell (granular, tubular) casts in the urine, of hypertension, of oedema (weight gain), but also by biological measure of renal function (creatinine clearance which reflects the glomerular filtration rate), significant proteinuria > 0.5 g per 24 hours recording or above 3+ on the labsticks. The presence of cellular casts in the urine corresponds to the presence of neutrophils or mixed red cells which precipitate in the renal tubular lumen and therefore appear in the urine.

Neurologic disorders can appear with various symptoms and the presence of neurological symptoms such as seizure or psychosis (that can be diagnosed as an SLE manifestation only after ruling out any other drugs or metabolic abnormalities) is a criteria for severe SLE.

Haematological disorders may be manifested by either a) a haemolytic anaemia which is in fact an autoimmune haemolytic anaemia characterised by the fall in the haemoglobin level and haptoglobin with increased levels of LDH or b) a thrombocytopenia which is defined by a fall in the number of platelets in the absence of any medication susceptible to explain these abnormalities.

The following biological criteria account for the diagnosis of SLE.

Immunologic disorder is the hallmark of SLE, which is due to the presence of pathogenic autoantibodies which recognise the self antigen (characteristics for identification of any individual) with a driven abnormal immune response against the self. The hallmark of these abnormalities is the appearance of autoantibodies such as:

- a) anti-DNA antibodies directed against the native deoxyribonucleic acid at a higher than the normal local level.
- b) antibodies directed against nuclear antigens and/or

c) antibodies against cardiolipin and other phospholipids, which can be also responsible for abnormality in the anticoagulation process with increased coagulation times and thrombotic manifestations (either arterial or venous). These antiphospholipid antibodies can be responsible for the appearance of a lupus anticoagulant, or account for a positive serological test for syphilis, whereas the specific syphilitic test with *Treponema pallidum* or fluorescent *Treponema* antibody absorption test is negative. This is why this is presented as a false positive serologic test for syphilis, whereas *Treponema pallidum* immobilisation or the first specific fluorescent antibody absorption tests are negative.

Presence of antinuclear antibody (antibodies directed against several components of the nucleus) alone accounts for a single criterion.

## FIRST LINE THERAPIES

The outcome of active severe SLE due to kidney, lung, heart or brain involvement, has improved in the past two decades due to early diagnosis and treatment with immunosuppressive agents combined with overall tighter control of general aspects such as blood pressure and infections. In this context, the first line therapies commonly used at aiming to induce remission within the first 6 to 9 months of disease flare are the corticosteroids in combination with other therapies.

Since the first NIH trial in 1970, which first demonstrated the superiority of cyclophosphamide (first orally and then iv) versus steroids in the treatment of SLE, every ten years shows significant improvement in the therapeutic strategies. Today the treatment of SLE relies on both on an induction and then a maintenance therapy, which may use various types of immunosuppressive regimen. First line therapies are used prior to consider HSCT, which will be indicated only for severe forms of the SLE disease:

Corticosteroids are the basis for the SLE treatment since they enable control of almost all acute flares of the disease, although currently associated with major side effects. All the other therapies added to the steroids aim to decrease the average daily dose of steroids. Steroids can be used orally or iv, at an oral dose from 0.1 to 1mg daily as induction and then decreased progressively over time. In case of flare of disease activity they can be used as iv bolus of methylprednisolone up to 500mg per day, generally on 3 successive days.

Androgens are a hormonal therapy which can be given to women with active SLE disease in order to counteract the oestrogen predisposition to the disease.

Antimalarial drugs (including chloroquine and hydroxychloroquine) have shown their benefit in the largest study to date in controlling the relapse of SLE following steroids.

Several types of immunosuppressive drugs are used with the aim to decrease the dose of steroids:

Azathioprine is a non specific purine inhibitor, which non specifically diminishes all the mitosis, and may thus induce adverse side effect on the blood cell and white cell counts with a fall in each cell blood count.

Cyclophosphamide is generally given as iv bolus monthly using various type of regimen, according to the ongoing protocol (NYH : originally iv monthly for six months with then maintenance quarterly every three months or at low dose; or according to the EuroLupus Protocol for three months every two weeks and then monthly up to six months).

Cyclosporin is an inhibitor of IL-2 production with renal toxicity and not commonly used in SLE.

Mycophenolate Mofetil is a specific inhibitor of de novo purine synthesis (inhibiting Inosine Monophosphate Dehydrogenase) and is used as one of the standard induction and maintenance treatments in SLE.

ivlg can be used on a monthly basis in cases of acute SLE flare of the disease, with either neurological or haematological manifestations.

Lymphocytapheresis or plasmapheresis are used to eliminate the auto-antibodies of patients' blood by aphaeresis or membrane dialysis.

Among other treatments there are several types of monoclonal antibodies directed against the T or the B cell receptors or the adhesion molecules involved in the T-B cell interaction and their co-stimulatory signals, like, for example, rituximab (anti CD20). They are mostly used off-label in many phase I-II trials to test their potential benefit as induction therapy.

However, there is still a subgroup of patients who do badly, such that even in tertiary referral centres there is still a 10 years mortality in SLE of 10%.

## DATE OF HSCT

With the aim of suppressing autoimmune disease in one concentrated effort rather than drawn out over a long period, an international effort over the past decade has studied the feasibility and the efficacy of autologous HSCT and has shown in phase I/II trials that many SLE patients responded to autologous HSCT, and that 55% achieved a durable remission with reduced or no immunosuppressive drug requirement.

Current results show that autologous HSCT results in amelioration of disease activity, improvement in serologic markers, and either in a stabilization or in an improvement of organ dysfunction. Review from the EBMT lupus data showed that one third of the patients with initial response to HSCT could relapse to some degree, but then responded to repeat exposure to immunosuppressive agents which pre-treatment had proven ineffective. In other words, a resetting of the autoaggressive process was achieved despite immunological reconstitution from an autologous immune system. This has been confirmed in multiple sclerosis, systemic sclerosis and more recently in juvenile idiopathic arthritis. Therefore, the question of post transplant immunosuppression is important: maintenance therapy in SLE relies on the lowest dose of steroids in combination of either an antimetabolite, such as azathioprine or more recently mycophenolate mofetil, or antimalarial drugs such as hydroxychloroquine or both in order to obtain a steroid sparing effect. Response to induction therapy is an important determinant of the long term outcome as well as the number of relapses during maintenance therapy.

## STATUS OF DISEASE AT MOBILISATION

## STATUS OF DISEASE AT HSCT

SLE clinical manifestations may vary in a single patient and among various types of patients from mild to moderate or severe, and therefore account for either isolated skin or arthritis manifestations with a few significant biological abnormalities or a multi systemic aggressive form with major organ involvement predominantly affecting the kidneys (various types of glomerulonephritis), the heart (polyserositis), the brain (psychological manifestations, seizure and encephalitis) which can hamper the vital prognosis.

**LUPUS NEPHRITIS** is an important prognostic factor of the SLE. It is diagnosed by histology of kidney biopsy samples according to the International classification (*J Am Soc Nephrol* 2004; 15: 241) as follows:

**Grade Histology**

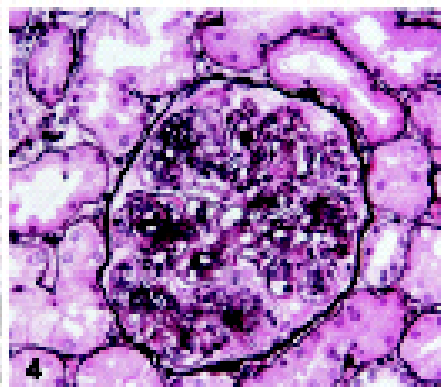
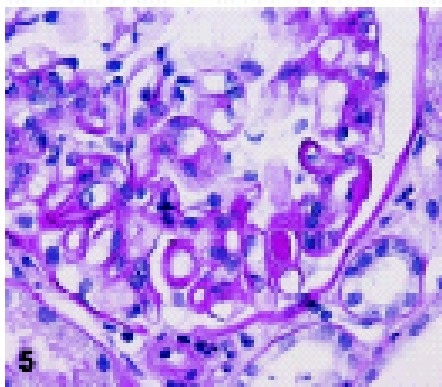
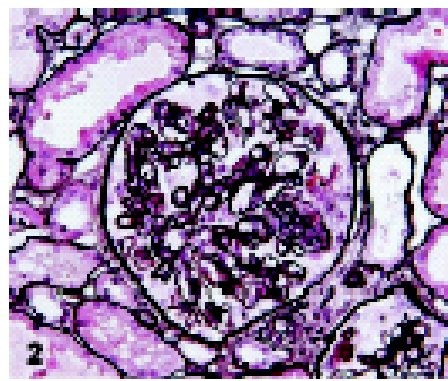
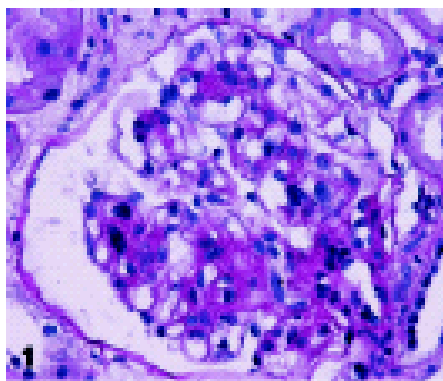
Class I	Minimal mesangial lupus nephritis
Class II	Mesangial proliferative lupus nephritis
Class III	Focal lupus nephritis <sup>a</sup>
Class IV	Diffuse segmental (IV-S) or global (IV-G) lupus nephritis <sup>b</sup>
Class V	Membranous lupus nephritis <sup>c</sup>
Class VI	Advanced sclerosing lupus nephritis

Indicate and grade (mild, moderate, severe) tubular atrophy, interstitial inflammation and fibrosis, severity of arteriosclerosis or other vascular lesions.

<sup>a</sup>Indicate the proportion of glomeruli with active and with sclerotic lesions.

<sup>b</sup>Indicate the proportion of glomeruli with fibrinoid necrosis and cellular crescents.

<sup>c</sup>Class V may occur in combination with class III or IV, in which case both will be diagnosed.

**SLEDAI**

At least, eight different types of index have been used in the past ten years. To characterise the severity of the disease, the most commonly used is SLEDAI (but you can also find the BILAG, SLICC, SELENA-SLEDAI, RIFLE etc...). The SLEDAI relies on the presence of several criteria corresponding to various clinical manifestations, each of which with its own scoring and a global score between 0 and 105.

- **brain manifestation** associated to the presence of disease or psychosis or organic brain syndromes or visual disturbances which are all clearly defined in the SLEDAI or cranial nerve disorder, or Lupus headache, or CVA.

Note that:

- An occasional seizure in a patient with chronic seizures does NOT count
- A seizure due to non-compliance with anti-epileptic does NOT count
- Chronic cognitive impairment does NOT count as organic brain syndrome
- Migraines or other intermittent headaches do NOT count as lupus headache

- **presence of vasculitis** may appear with various clinical manifestation from the ulceration to gangrene or periungual infarction which may be seen clinically or on the biopsy or angiography at any site of the body.
- **rheumatological manifestations** may associate the presence of arthritis with at least two joints with pains and signs of inflammation or of myositis characterised by clinical manifestations plus evidence of abnormal biological signs, creatine phosphokinase and aldolase as specific enzymes of the muscles. The electromyogram is a way to measure the diffusion of the conduction at the level of the muscles and to characterise the presence of inflammation and myositis.
- **renal manifestations** may appear as various types of biological symptoms with presence of casts -due to the precipitation of protein mixed up with granular and red blood cells in the tubules- that may appear in the urine. Note that in order to record as Lupus:
  - Hematuria requires proteinuria
  - Pyuria requires proteinuria
  - Or, a recent renal biopsy must be positive
- **skin manifestation** is with new rash or sustained alopecia
  - Rash: ONGOING inflammatory lupus rash or NEW
  - Alopecia: ONGOING abnormal, patchy, or diffuse loss of hair or NEW
  - Mucosal ulcers: ONGOING oral or nasal ulcerations or NEW

The presence of pleuritis such as **pleurisy** or **pericarditis**, each of them accounting for a criterion.

**The presence of abnormal biological** sign such as low complement. Complement is a protein synthesised at the liver level, which is associated closely with the immune response. A decreased level of complement can be genetical or acquired in the context of autoimmunity.

#### LABORATORY VALUES

For all these reasons, it is important to report several parameters before the transplant and through out the follow up, such as the haematology parameters including haemoglobin, erythrocyte sedimentation rate, platelets, and white blood cells.

To monitor kidney function, serum creatinine should be reported. Creatinine is a substance produced by the muscle which is filtered, reabsorbed and secreted by the tubular kidney. Therefore, the serum creatinine level in a patient is a good indication of renal function. However, in patients with very high or low muscle mass, creatinine clearance is a better indication of kidney function. Because of this total urinary protein excretion, expressed in mg per 24 hours is also requested, as is the level of complement and the presence of various types of antibodies.

#### PATIENT'S SELF ASSESSMENT

Several indexes have been developed to assess quality of life among them:

**SF 36** is a complex multi questionnaire form with a score ranging from 0 to 100 which is separated in eight different domains by physical function, emotional function, bodily pain, mental health, vitality and general health.

**Health Assessment Questionnaire** is also a multiple choice questionnaire.

#### Further reading

Doria A, Laccarino L, Ghirardello A, Zampieri S, Arienti S, Sarzi-Puttini P et al. Long-Term Prognosis and Causes of Death in Systemic Lupus Erythematosus. *Amer J Med* 2006; 119, 700-706.

Moss KE, Ioannou Y, Sultan SM, et al. Outcome of a cohort of 300 patients with systemic lupus erythematosus attending a dedicated clinic for over two decades. *Ann Rheum Dis*. 2002; 61:409-413.

Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40:1725

SPECIFICATIONS  
OF THE DISEASE

## JUVENILE IDIOPATHIC ARTHRITIS

## DIAGNOSIS

**SUBCLASSIFICATION AT DIAGNOSIS**

The main aspect of the disease is the presence of chronic arthritis. Arthritis is defined as joint swelling and/or pain on movement or palpation of the joint. The duration of the arthritis must be at least 12 weeks. Known causes of joint swelling such as infections, malignancies or metabolic diseases must be excluded.

The ILAR (International League Against Rheumatism) subclassification of Juvenile Idiopathic Arthritis (JIA) is nowadays the one most commonly used (reference: Journal of Rheumatology 2004; 31: 390-392). Of these the polyarticular forms (with or without rheumatoid factor) and the systemic onset forms are the most severe subtypes.

JIA is a clinical diagnosis. Biopsy confirmation is not necessary. Often, however, arthroscopy is performed to exclude other causes of joint swelling.

ILAR subclassification:

1. **oligoarticular:** arthritis affecting 1 to 4 joints during the first 6 months of the disease.
2. **extended oligoarticular:** affecting a total of more than 4 joints after the first 6 months of disease.
3. **RF positive polyarticular:** arthritis affecting 5 or more joints during the first 6 months of the disease. A test for rheumatoid factor (RF) is positive.
4. **RF negative polyarticular:** arthritis affecting 5 or more joints during the first 6 months of the disease. A test for rheumatoid factor (RF) is negative
5. **Systemic JIA:** Arthritis in 1 or more joints with or preceded by daily spiking fever of at least 2 weeks duration and accompanied by 1 or more of the following: Pink evanescent rash, generalised lymph node enlargement, hepatosplenomegaly or serositis.
6. **Psoriatic JIA:** Arthritis and psoriasis and at least 2 of the following: dactylitis, nail pitting, psoriasis in a first-degree relative.
7. **Enthesitis related JIA:** Arthritis and enthesitis and at least 2 of the following: sacro-illitis, presence of HLA-B27, onset in males over 6 years of age, presence of acute anterior uveitis, history of ankylosing spondylitis or sacro-iliitis with inflammatory bowel syndrome in first-degree relative
8. **Unclassified JIA:** arthritis that fulfils criteria in no category or in 2 or more of the above categories

The exact diagnosis has to be given in the pre-transplantation letter.

**COURSE OF THE DISEASE UNTIL MOBILISATION/TRANSPLANT**

Schneider criteria refer to the persistence of thrombocytosis ( $>600$ ) for more than 6 months after onset and use of corticosteroids to control fever.

Disease progression on therapy is defined as presence of elevated disease activity parameters, also called the core set criteria for JIA. These consist of 1) the number of joints with active arthritis 2) the Physician's Global Assessment (PGA) of disease activity, 3) number of joints with limitation of movement 4) the Erythrocyte Sedimentation Rate (ESR), and 5) the Childhood Health Assessment questionnaire (CHAQ) for assessment of patient reported disability and disease severity. These tests are internationally validated and used by every paediatric rheumatologist. Details are given in the appendix B1 to B4 of the MED-B form.

**AUTOANTIBODIES**

Here serological tests for Rheumatoid factor (RF) or Antinuclear Antibodies (ANA) can be noted.

## FIRST LINE THERAPIES

Here an overview can be given for the drugs used for the current disease prior to transplant. For the second line drugs (such as Methotrexate) and immunosuppressants the starting date is also required.

## STATUS OF DISEASE AT MOBILISATION/COLLECTION

## STATUS OF DISEASE AT HSCT

This section must be completed at the actual moment of peripheral stem cell mobilisation or HSCT respectively.

### DISEASE STATUS

Please give the results of active joint count, limitation of movement, morning stiffness (details in appendix) and the haematological and biochemical values, and autoantibody status.

**RADIOGRAPHIC EVALUATION:** no simple method exists to quantify disease activity on radiographs. Simply note presence of erosions or presence of advanced skeletal age (which is caused by chronic inflammation)

### HEALTH ASSESSMENT QUESTIONNAIRE

Please give the results of the Childhood Health Assessment questionnaire (CHAQ) for assessment of patient reported disability pain and disease severity. These are reported on Visual Analogue Scales which usually range from 0 (no disability, pain or severity) to 100 (maximal disability, pain or severity).

**Physician's assessment** This is the overall disease activity to the opinion of an experienced paediatric rheumatologist. This value is reported on Visual Analogue Scales which usually range from 0 (no disease activity) to 100 (maximal severity).

### DISEASE RESPONSE TO THE MOBILISATION

#### BEST DISEASE STATUS

Here the internationally used criteria for JIA disease response to treatment must be given. Disease response to treatment is defined as a 30% improvement of at least 3 parameters. Of the remaining parameters 1 may be worsened by up to 30%.

### ADDITIONAL DISEASE MODIFYING DRUGS AND IMMUNOSUPPRESSANTS FOR JIA.

Here additional therapy used during conditioning can be specified. For instance use of extra corticosteroids and cyclosporin A for prophylaxis of haemophagocytosis (also called Macrophage Activation Syndrome)

SPECIFICATIONS  
OF THE DISEASE

## MULTIPLE SCLEROSIS

## DIAGNOSIS

**MAIN DIAGNOSIS**

The date of diagnosis is the date when patient would fulfill any criteria (radiologic, laboratorial or clinical) for the diagnosis of MS. Multiple Sclerosis (MS) is a chronic, inflammatory, demyelinating disease of the central nervous system, and is one of the most common causes of neurological disability in young adults.

Poser criteria are diagnostic criteria for MS [reference: Poser CM, et al, Annals of Neurology, 1983, 13 (3): 227–31].

## FIRST LINE THERAPIES

This section of the form is to specify which treatment the patient received since diagnosis of MS. The treatments considered here use disease-modifying drugs, or drugs specifically given to delay progression of the disease. Treatment to improve symptoms during acute disease exacerbations, also termed attacks or disease relapses are not considered here. For example: when patients with MS have acute exacerbation of neurologic symptoms and fever, they might be treated with pulse doses of corticosteroids for a short period of time to improve the symptoms during these acute disease exacerbations. If patients are on chronic doses of corticosteroids, this should be marked as treatment in this section, short courses during acute exacerbation should not be marked here.

There are other treatment modalities such as Plasmapheresis (procedure used to remove pathogenic humoral factors, among them suspected auto-antibodies directed against the myelin sheath) – Reference:

Faissner S, Nikolayczik J, Chan A, Hellwig K, Gold R, Yoon MS, Haghighi A.

Plasmapheresis and immunoadsorption in patients with steroid refractory multiple sclerosis relapses. J Neurol. 2016 Jun; 263(6):1092-8.

For date of treatment, use the first date the patient received disease modifying drugs or other type of treatment since the diagnosis of MS.

## STATUS OF DISEASE AT MOBILISATION/COLLECTION

**Clinical evaluation**

This question should be reviewed with the neurologist consultant to the transplant center. The assessment should be made less than 4 weeks prior to mobilisation.

**Scripps**

Currently it is not used in clinical practice, but it is left here for reasons of consistency with past data.

**Kurtz functional systems**

The Functional System Scores is assessed by a neurologist and summarizes the specific neurologic function disability.

**Kurtz expanded disability status scale (EDSS)**

The EDSS is a composite assessment, performed by the neurologist that illustrates the degree of disability associated with MS. It provides a useful snapshot of the disease status of a patient at a given time and a composite picture of the disease course over time. The EDSS is universally used in clinical trials [reference: Kurtzke JF. Neurology 1983; 33: 1444-52].

### Multiple Sclerosis Functional Composite Measure (MSFC)

The MSFC comprises quantitative functional measures of three key clinical dimensions of MS: leg function/ambulation, arm/hand function, and cognitive function. Scores on component measures are converted to standard scores (z-scores), which are averaged to form a single MSFC score. – Reference:

- Fischer JS, Rudick RA, Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite Measure (MSFC): an integrated approach to MS clinical outcome assessment. National MS Society Clinical Outcomes Assessment Task Force. *Mult Scler*. 1999 Aug;5(4):244-50.

- Rudick RA, Polman CH, Cohen JA, Walton MK, Miller AE, Confavreux C, Lublin FD, Hutchinson M, O'Connor PW, Schwid SR, Balcer LJ, Lynn F, Panzara MA, Sandrock AW. Assessing disability progression with the Multiple Sclerosis Functional Composite. *Mult Scler*. 2009 Aug;15(8):984-97.

### MRI brain scan

Magnet resonance imaging (MRI) is an important assessment for patients with MS. It is used frequently to assess burden of disease and often disease progression is associated with increase number and size of brain lesions seen on MRI. If several MRI tests were performed use the MRI date that is closest to the mobilisation date. Details from the MRI radiologic report can be used to answer these questions.

## STATUS OF DISEASE AT HSCT

### DISEASE COURSE

Disease course evaluation requires an assessment of the pace, progression and other disease manifestations during a period of time, here two years prior to presentation. The pattern and course of MS are categorized as follows [reference: Lublin FD et al, *Neurology* 1996; 46: 907-11]

Progressive relapsing (PRMS) is characterized by continuous disease progression with clear acute disease exacerbation episodes, patients tend to have worsened disease manifestations after recovery from an acute disease exacerbation.

Progressive Relapsing MS (PRMS) accounts for 5% of MS patients. Patients with clinically definite MS have typical white matter lesions on Magnetic resonance imaging (MRI) in over 90 percent of cases.

Primary progressive (PPMS) is characterized by continuous disease progression without distinct acute disease exacerbations.

Primary Progressive MS (PPMS) accounts for 10-15% of cases. These patients have a more even sex distribution, the disease begins later in life (mean age 40 years), and disability develops faster compared to patients with RRMS.

Secondary progressive (SPMS) is characterized by acute disease exacerbations periods where there is disease progression after acute disease exacerbations.

SPMS produces a greater amount of fixed neurologic disability than RRMS. Approximately 50% of patients with RRMS will have developed SPMS after 15 years, and longer follow up points indicate that the great majority of RRMS ultimately evolves into SPMS; thus SPMS appears to represent a late stage of the same illness as RRMS.

Relapsing remitting (RRMS) disease course is characterized by a series of periods with acute disease exacerbations that resolve completely without worsening of the neurological functions.

Relapsing Remitting MS (RRMS) accounts for 85% of MS cases at onset and is characterized by discrete attacks (relapses), consisting of acute or sub-acute clinical dysfunction, that generally evolve over days to weeks, followed by a complete or partial recovery (remission) over the ensuing weeks to months. Between attacks patients are neurologically stable.

This question should be reviewed with the neurologist consultant to the transplant center.

Did the patient progress during the 2-years prior to mobilisation/HSCT?

If the answer is positive, specify the number of relapses/progressions. These consist of acute disease exacerbations, characterized by sudden worsening of neurologic symptoms or development of new neurologic symptoms accompanied or not by fever.

This question should be reviewed with the neurologist consultant to the transplant center.

**CLINICAL EVALUATION****MRI BRAIN SCAN DONE**

See above under MOBILISATION/COLLECTION

## ADDITIONAL TREATMENT POST-HSCT

Specify whether the patient received any disease modifying treatment for MS. Medications for acute disease exacerbation such as pulse doses of corticosteroids should not be considered as MS treatment in this question.

Specify the reason for initiating disease modifying treatment for MS.

See FIRST LINE THERAPIES above.

## STATUS AT A 100 DAYS POST-HSCT

See STATUS OF DISEASE AT MOBILISATION /COLLECTION above. For baseline refer to “STATUS AT TRANSPLANT”

*The response date is the date that the sample or image was taken for assessing the response*

## FOLLOW UP

## MULTIPLE SCLEROSIS

For most questions, see STATUS OF DISEASE AT MOBILISATION / HSCT or FIRST LINE THERAPIES above.

## FIRST EVIDENCE OF DISEASE WORSENING SINCE LAST HSCT

Relapses are acute disease exacerbations, also termed attacks. Specify whether the patient had any acute disease exacerbations since the last report. The date of the first acute disease exacerbation should be included and the overall number of these exacerbations since last report should be included.

Continuous worsening or disease progression of MS, is characterized by worsening disability due to worsening symptoms or development of new neurologic symptoms. Progressions is often corroborated by the presence of new abnormalities seen in the brain MRI.

SPECIFICATIONS  
OF THE DISEASE

## SOLID TUMOURS

## DIAGNOSIS

Solid Tumours are a group of malignancies presenting with masses internal or external to organs such as breast, ovarian or lung carcinoma. Although lymphomas may present with solid masses internally or externally, they are categorised under a different section because lymphomas are related to lymphatic system and investigated under the lymphoma working party.

**VSOLTUMO** Select the sub classification that is appropriate for the tumour and check the box next to it. If diagnosis is not listed, specify the diagnosis in clear.

## CLINICAL CLASSIFICATION AT DIAGNOSIS

**Clinical TNM classification:** (see patient's chart) Clinical TNM classification is used by medical oncologists and pathologists to define the stage of the disease accurately. Most of the solid tumours have different TNM classification which are not transferable from tumour to tumour. Therefore when you fill the section on TNM you have to use the TNM classification specific for that diagnosis. There are books or related materials which can be consulted, for example, medical oncology textbooks and manuals. Note that if both clinical and pathological TNM tests are done for the patient (usually this is the case for Breast Cancer), the pathological ones have to be preferred and reported.

TNM stands for:

**VTNMT** T: defines size of the tumour as cm or number of tumours. According to the size or number of tumours, you have to mark either 1,2,3 or 4. X indicates assessment not possible.

**VTNMN** N: defines the degree / spread of metastasis to the lymph nodes. According to the spread or size of nodes involved you have to mark either 1,2 or 3. Note that not all grades are used in all solid tumours. If there are no nodes 0 has to be marked. X indicates assessment not possible

**VTNMM** M: defines number of metastasis. If patient has metastasis mark 1. X indicates assessment not possible.

In addition to the TNM classification, further staging information is requested for breast carcinoma and germ cell tumour:

**VINFLAM** BREAST CARCINOMA

The classification presented here is clinicopathological, subdividing the disease into inflammatory and non inflammatory:

- Inflammatory: in general staged as stage IIIB which is a small proportion of breast carcinoma.
- Non Inflammatory: encompasses all remaining subsets including metastatic.

**Example of TNM for Breast Cancer:**

The definitions for classifying the primary tumour (T) are the same for both the clinical and the pathological classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2 or T3). If the other measurements, such as mammography or pathology, are used, subtypes of T1 can be used.

**Primary Tumour (T)**

**TX** Primary tumour cannot be assessed

**T0** No evidence of primary tumour

**Tis** Carcinoma *in situ*: Intraductal carcinoma, lobular carcinoma *in situ*, or Paget's disease of the nipple with no tumour.

**T1** Tumour 2 cm or less in greatest dimension

T1mic . Microinvasion 0.1 cm or less in greatest dimension

T1a Tumour more than 0.1 cm but not more than 0.5 cm in greatest dimension

T1b Tumour more than 0.5 cm but not more than 1 cm in greatest dimension

T1c Tumour more than 1 cm but not more than 2 cm in greatest dimension

**T2** Tumour more than 2 cm but not more than 5 cm in greatest dimension

**T3** Tumour more than 5 cm in greatest dimension

**T4** Tumour of any size with direct extension to (a) chest wall or (b) skin, only as described below.

T4a Extension to chest wall

T4b Oedema (including peau d'orange) or ulceration of the skin of the breast or satellite skin nodules confined to the same breast

T4c Both (T4a and T4b)

T4d Inflammatory carcinoma

Note: Paget's disease associated with a tumour is classified according to the size of the tumour.

**Regional Lymph Nodes(N)**

**NX** Regional lymph nodes cannot be assessed (e.g., previously removed)

**N0** No regional lymph node metastasis

**N1** Metastasis to movable ipsilateral axillary lymph node(s)

**N2** Metastasis to ipsilateral axillary lymph node(s) fixed to one another or to other structures

**N3** Metastasis to ipsilateral internal mammary lymph node(s)

**Distant Metastasis (M)**

**MX** Distant metastasis cannot be assessed

**M0** No distant metastasis

**M1** Distant metastasis (includes metastasis to ipsilateral supraclavicular lymph node(s))

**VSTGDST**

**Stage of disease:** Most of the solid tumours in the field of medical oncology are staged 1 to 4, sometimes 5. Also histological grading is done 1 to 4. This has to be marked appropriately according to the stage of disease. If stage is unknown or not done check the appropriate box.

**EXAMPLE:** Correspondence between TNM classification and staging for breast carcinoma.

**Stage Grouping**

<b>Stage 0</b>	Ties	N0	M0
<b>Stage I</b>	T1*	N0	M0
<b>Stage IIA</b>	T0	N1	M0
	T1*	N1	M0
	T2	N0	M0
<b>Stage IIB</b>	T2	N1	M0
	T3	N0	M0
<b>Stage IIIA</b>	T0	N2	M0
	T1*	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
<b>Stage IIIB</b>	T4	Any N	M0
	Any T	N3	M0
<b>Stage IV</b>	Any T	Any N	M1

\*Note: T1 includes T1 mic

**DISHGRD Histological grading:**

Most of the solid tumours also have a histological grade, usually graded from 1 to 3, occasionally 4. A higher number indicates a more malign tumour. For example, a grade 3 tumour has more malignant histopathological features than a grade 2 or 1 tumour for the same histology. This means that tumours with a higher histological grade will have worse prognosis than those with low grade ones. If histological grading is unknown or not done check the appropriate box.

**VHISTSGD Histological subclassification**

Some solid tumours have histological subtypes. For example, non-small cell carcinoma has three different subtypes, which are squamous cell, large cell and adenocancer; breast cancer has two main subtypes which are infiltrative ductal carcinoma and lobular carcinoma. Write in clear the subtype.

**VESTROGR Receptor status:** (see laboratory or pathology reports for the results). Receptors are specific

**VPROGESR** molecules which are carried on the surface of cells, including tumour cells, which bind to particular compounds. Breast carcinoma cells have several receptors which can characterise it. The most common receptors are oestrogen receptors (ER) which bind oestrogen and progesterone receptors (PgR) which

**VESRCVAL** bind progesterone. Pathologists report receptor positivity as a percentage, for example, 70 % ER+, 10%

**VPRGRCVA** ER+. This positivity is measured by immunohistochemical methods.

### Histological subclassification for breast carcinoma

In this section we request additional information to describe in more detail the subclassification of breast carcinoma. The information should be in the pathology reports in the patient's file.

**Lymph nodes** are special stations normally less than 10 mm in diameter depending on the location, controlling the lymphatic circulation, which may respond to microorganisms, tumour cells etc. Main lymph nodes are normally located in the neck region, axilla and inguinal area.

Axillary lymph nodes:

**VNISOBRC** N° Isolated: number of lymph nodes obtained by surgeon during axillary dissection.

**VNINVBR** N° involved: how many of the above lymph nodes had tumour involvement.

**VSBR** S.B.R. (Scarff and Bloom Richardson): This is used for histological grading. Grading is being done by scoring whether tubular structures, mitosis, necrosis and pleomorphism are seen or not.

**VDUCTAL** **VLOBULAR** Ductal carcinoma and Lobular carcinoma: Breast cancer has two common histological subtype which are ductal and lobular carcinoma. Ductal carcinoma is seen more frequently than lobular carcinoma. Please, specify the type here

### **VHSTCLAS** GERM CELL TUMOURS

Indicate whether the histological subclassification is **Seminoma** or **Non-seminoma**. Seminoma (pure seminoma) is when 100% of the tumor is seminoma, all others are **Non-seminoma**; other investigators may consider a mixed category when seminoma and non seminoma parts are present but treatment options and prognosis depend only on the classification in two subtypes: **Seminoma** and **Non-seminoma**.

### **VCHROMOS** CYTOGENETICS (**CHROMOSOMAL STUDY**)

Indicate here any known cytogenetic abnormality such as chromosome related aberrations, deletions, etc. If no cytogenetics has been done, please check "Not done". If cytogenetics has been performed and no abnormalities found, please indicate so.

### **MOLEBIO** MOLECULAR BIOLOGY

Oncogenes are molecular markers which are over expressed in some solid tumours. These oncogenes are determined by molecular biology laboratories which have expertise in this field. Oncogenes are used for diagnosis and sometimes to follow-up the disease after treatment. Indicate whether molecular biology studies have been done to identify these oncogenes. If they have been done, and no oncogenes have been found the result would be "Normal", if on the contrary oncogenes have been found, the result would be "Abnormal". If no molecular biology has been done, please check "Not done"

Whenever a molecular study has been done, whether it is normal or abnormal, indicate the type of oncogenes that have been studied.

**MOLOTH** If oncogenes have been identified, write down the name of the oncogene. For example, if a breast cancer patient has BRCA1 or BRCA2 genes, this has to be noted in the molecular biology section. If molecular biology analysis has been performed and no abnormalities found, please indicate so.

## TREATMENT GIVEN BEFORE THIS HSCT

*i.e. first therapeutic approach to the patient, but If this registration pertains to a second or subsequent transplant the therapy number should be counted since last reported transplant.*

Marrow or stem cell transplantation in solid tumours may still be of an experimental nature such as for breast, ovarian and lung cancer. Therefore, there are many ongoing trials in order to investigate the efficacy of this approach in patients with solid tumours. These are established protocols which are produced by scientific committee as well as reviewed and approved by institutional review board and ethical committees, such as those run under the Solid Tumours Working Party sponsorship.

**FIRST LINE TREATMENT**

First line treatments for solid tumours may cause confusion for data managers who are also reporting transplants performed for other indications. As opposed to primary treatment for most haematological malignancies, primary treatment in solid tumours is a surgical approach rather than a medical one. The primary treatment should be clearly described in the patient's chart.

**MODALITIES**

**VADJUVAN** Modality refers to the type of treatment. This can be adjuvant chemotherapy (additional treatment given immediately after surgical removal of the tumour, in the absence of visible disease), neo-adjuvant  
**VNEODAJU** chemotherapy (treatment given immediately before surgery to decrease the size of the tumour and facilitate  
**ETC .** its surgical removal), other chemotherapy, surgery or radiotherapy.

**SURTMP STATUS OF DISEASE AFTER FIRST LINE TREATMENT** (see patient's chart)

This defines the response of disease to primary treatment. After primary treatment, tumour can be completely eradicated, microscopic disease (disease is determined by biopsy) may remain or macroscopic disease may remain.

If there is any microscopic or macroscopic disease left we cannot talk about complete removal or complete remission. If primary treatment is chemotherapy or radiotherapy and disease is still remaining this status is called primary refractory disease. If primary treatment is surgery and disease remains after surgery, this status is called partial remission (for macroscopic disease).

Complete Remission:	the patient has achieved complete absence of disease.
Partial Remission:	disease burden is reduced by more than 50%.
Stable Disease:	no change, disease burden did not change after treatment.
Refractory Disease:	disease progressed despite treatment.
Not Evaluable:	burden of disease cannot be measured.

**VPRETRAT ADDITIONAL LINES OF TREATMENT BEFORE THIS HSCT FOR RELAPSED/REFRACTORY DISEASE**

Relapse after primary treatment means patients had complete remission clinically and pathologically but relapsed after that in a local or distant site.

The reappearance of a marker is *per se* no evidence of relapse (WHO and RECIST criteria).

**VOThERT** Indicate here if additional treatment was given after first relapse or for refractory disease.

## TREATMENT HISTORY BEFORE HSCT

## STATUS OF DISEASE AT HSCT

**VDISESTA STATUS OF DISEASE AT TRANSPLANTATION** (see patient's chart)  
 The definitions of status at transplant for solid tumours are as follows:

<b>Adjuvant</b>	Adjuvant therapy is an additional treatment given immediately after surgical removal of the tumour, in the absence of visible disease, in order to eliminate any residual (invisible)
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tumor. An HSCT can be part, along with conventional chemo (adjuvant or neo-adjuvant), radiotherapy and targeted therapies (including hormonal treatment in the case of breast cancer), of an adjuvant program. In these cases, the HSCT is usually preceded by some cycles of conventional chemotherapy and followed, if clinically indicated, by radiotherapy/targeted therapies. An HSCT given within such a program is considered Adjuvant. Metastatic patients (any status) should never be considered as adjuvant.

**Complete remission (CR)** The patient has achieved complete absence of disease prior to transplant and the transplant is not part of any adjuvant therapy (above).

If the patient is in complete remission, please indicate the number of this CR and whether the CR is confirmed or unconfirmed:

**VCRCONF1**

**CR confirmed** - no abnormalities detected in the scan  
**CR unconfirmed (CRU)** - persistent scan abnormalities of unknown significance

**First partial remission (PR)** The patient has obtained a reduction of more than 50% in the disease burden after the initial treatment.

**Primary refractory Disease (RD)** The patient has not achieved any of the above types of response with any therapy until now.

**Relapse** The patient obtained CR with a previous therapy, after which he/she relapsed.

If the patient is in relapse, please indicate the number of the relapse, and the sensitivity to the treatment given for this relapse.

**VSENSIT**

**Sensitive (SR)** The patient achieves a reduction of more than 50% in the disease burden after treatment for this relapse.  
**Resistant (RR)** The patient has not achieved a reduction of more than 50% in the disease burden after treatment for this relapse.  
**Untreated** The patient has not been treated for this relapse.

**Upfront (Never treated)** The patient has never been treated for this disease. The high dose therapy is part of the overall treatment strategy.

**VORGANIN  
ETC**

**ORGAN(S) INVOLVED:** (see patient's chart)  
 This section defines organs involved with disease during relapse.

## RESPONSE OF DISEASE

**VRESPST** Definitions as for "Status of disease at transplantation" section, above.

### Med-A only

#### Current disease status

You must tick only one box. Indicate if the patient is in complete remission or not. For baseline refer to "STATUS AT TRANSPLANT"

*The response date is the date that the sample or image was taken for assessing the response*

#### Date achieved

If the patient is in CR, enter the date it was achieved or assessed.

#### Date assessed

If the patient is not in CR enter the last date the patient's disease status was recorded.

## ALL DISEASES

## ALLOGRAFT

## PATIENT

Allograft indicates that the patient is the recipient of stem cells taken from another person, who is called the donor. If the donor is an identical twin, the transplant is called syngeneic. This form should be filled also for syngeneic transplants.

VHIVPAT  
VCMVPAT  
ETC

**ANTIBODIES IN THE PATIENT**

(before transplantation)

**ANTIGENS**

(if applicable)

Antibodies are proteins made by a patient after exposure to an infectious agent or 'antigen' e.g. bacteria, virus, toxoplasma etc or after vaccination. You may find the antibody status of the patient in the patient's file under serology, virology or bacteriology. The antibody may be reported as IgG or IgM or both ("Ig" stands for immunoglobulin). An isolated positive IgG antibody means an infection (or vaccination) in the past, a positive IgM antibody (plus or minus positive IgG) indicates a recent infection (or vaccination). If either or both are positive, please answer "Positive"

Antigen testing detects the virus itself. The two viruses CMV and EBV remain "hidden" in the body after an infection and cannot be eliminated (the patient is a 'carrier'). If the antibodies are positive you know that the virus is also present; for this reason the results of testing for antigens for these viruses are not requested. Due to the immunosuppression associated with transplantation, a (sometimes lethal) reactivation of the infection can occur. During the transplantation period, antibody positive patients should be monitored for reactivation.

For hepatitis B and C, the situation is different. In most cases the virus is eliminated from the body by the antibodies and the immune system. If one of those viruses remains present (antigen = positive), the patient is a 'carrier' and may be treated before transplantation with virostatics to eradicate the virus (this is not possible for CMV and EBV).

Virus test abbreviations:

s = surface

c= central or cytoplasmic

(V = virus but it seems to be used less now)

HBVs antibodies = Hepatitis B virus surface antibodies (*anti - HBs*)

HBVs antigen = Hepatitis B virus surface antigen (*HBsAG*)

HBVc antigen = Hepatitis B virus central (or cytoplasmic) antigen

HBVe antibodies/HBVe antigen = is a viral protein associated with HBV infections. Unlike the surface antigen, the e-antigen is found in the blood only when there are viruses also present.

**PRE-TRANSPLANT HISTORY OF DOCUMENTED INVASIVE FUNGAL INFECTION SINCE INITIAL DIAGNOSIS**

VPTCANDI  
VPTASPER

Fungal infections are a common cause of fever in immunosuppressed patients and can be fatal. They are often difficult to diagnose and anti-fungal treatment may be commenced without definite proof of the presence of the fungus. Patients may respond well to the anti-fungal treatment and in this case there may be a strong suspicion that the cause of the fever was indeed fungal. However the presence of the fungus was not documented.

To answer Yes to this question there must have been bacteriological evidence that the fungus was present in the impaired organ. If the patient was previously treated in another centre this information may be found in the pre-transplantation letter or letter from referring centre. *Pneumocystis carinii*, although strictly speaking is not considered to be a fungus, is included here because it is also common in the immunosuppressed patient.

CHNRD

**PERFORMANCE SCORE**

The Karnofsky and Lansky are standard performance scales used to measure the wellbeing of a patient. The Karnofsky 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 represent the situation at start of conditioning, 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 this manual.

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**WEIGHTB** Weight (kg) : ..... Height (cm) : ..... **VBQM**

The values should represent the situation at start of conditioning.

**COMORBID** **COMORBID CONDITIONS**

Comorbid conditions are those conditions which are likely to affect the outcome of the HSCT but which may not be directly related to the diagnosis indication for transplant.

Ensure an answer is only given if the comorbid condition fits the definition found in the form itself. Do not give a positive answer if the condition exists in a milder way than defined (for example, minor obesity not reaching the required index). The answers should represent the situation at start of conditioning unless otherwise stated in the definitions below. Infections: Preventative treatment in the absence of detected infection should not be added to the comorbidity

The Hematopoietic Cell Transplant-Co-morbidity Index (HCT-CI)

The following worksheet can be used to calculate the HCT-CI as reported by Sorror et al., Blood, 2005 Oct 15; 106(8): 2912-2919. Although the HCT-CI score is not reported on the forms, the HCT-CI worksheet may assist centres in determining which diseases or conditions to report in the co-morbid conditions

Directions for completing the HCT-CI worksheet:

1) If the recipient has a documented history of any of the conditions listed in the “definition/compartments” column, check the corresponding “yes” box in the Comorbidity Index.

Co-morbidity	Definition/compartme
1. Arrhythmia	- Atrial fibrillation* - Atrial flutter* - Sick sinus syndrome* - Ventricular arrhythmia*
2. Cardiovascular	- Coronary artery disease* - Congestive heart failure* - Myocardial infarction* - Ejection fraction $\leq 50\%$ § or shortening fraction in children $< 28\%$
3. Inflammatory bowel disease	- Crohn's disease* - Ulcerative colitis*
4. Diabetes	- Treated with insulin or oral hypoglycemic drugs§
5. Cerebro-vascular	- Transient ischemic attacks* - Cerebro - vascular ischemic or hemorrhagic stroke*
6. Depression/anxiety	- Requiring psychological consultation and/or specific treatments§
7. Hepatic - mild	- Chronic hepatitis§ - Bilirubin $> \text{ULN} - 1.5 \times \text{ULN}$ § - AST/ALT $> \text{ULN} - 2.5 \times \text{ULN}$ §
8. Obesity	- Body mass index $> 35$ (adults)§ - Body mass index - for - age $\geq 95\%$ percentile (children)§
9. Infection	- Requiring anti - microbial treatment before, during, and after the start of conditioning§
10. Rheumatologic	- Requiring Treatment*
11. Peptic ulcer	- Confirmed by endoscopy and requiring treatment*
12. Renal	- Serum creatinine $> 2\text{mg/dl}$ (or $> 177\mu\text{mol/L}$ )§ - On dialysis§ - Prior renal transplantation*
13. Pulmonary - Moderate	- DLco corrected for hemoglobin 66 - 80% of predicted§ - FEV1 66 - 80% of predicted§ - Dyspnea on slight activity§
14. Pulmonary - Severe	- DLco corrected for hemoglobin $\leq 65\%$ of predicted§ - FEV1 $\leq 65\%$ of predicted§ - Dyspnea at rest or requiring oxygen therapy§
15. Heart valve disease	- Except asymptomatic mitral valve prolapse§
16. Prior solid malignancy	- Treated with surgery, chemotherapy, and/or radiotherapy, excluding non - melanoma skin cancer*
17. Hepatic - moderate/severe	- Liver cirrhosis§ - Bilirubin $> 1.5 \times \text{ULN}$ § - AST/ALT $> 2.5 \times \text{ULN}$ §

\*Diagnosed at any time in the patient's past history

§Detected at the time of pretransplant assessment - ULN indicates upper limit of normal; DLco, diffusion capacity of carbon monoxide;

Please note that between results from 2 different types of tests performed (One is the DLco SB (=transfer factor), the other one is the DLco/VA (=transfer coefficient), the correct one to choose is the **DLco SB (= transfer factor)**.

FEV1, forced expiratory volume in one second;

AST, aspartate aminotransferase; and ALT, alanine aminotransferase

## DONOR AND STEM CELL SOURCE

### VMULTDON Multiple donors

Indicate whether products used in this transplant belonged to more than one donor.

Although it is rare to have multiple donors where the source of the cells is bone marrow or peripheral blood, this is not the case when the transplant involves cord blood (CB): the peripheral blood may be collected from one donor and the cord blood from another one, for example, and multiple CB units (CBU) being used in one HSCT is common.

It may also happen that there is only one (same) donor even if there are two sources: for example, the CB and the PB were collected from the same donor. This case is possible only for related transplants when the donors are children (CB is collected and preserved in a local CB Bank, PB is collected later and the transplant is done with the infusion of stem cells from CB+PB).

#### IMPORTANT NOTE:

**The forms provide space to fill in up to 2 products per donor, and up to 2 donors. If there were more products per donor, or more than 2 donors, copy the section as many times as necessary and fill in the information for each individual donor/product separately.**

### DONORID2 Identification of Donor or Cord Blood Unit given by the centre

If the donor comes from an unrelated donor registry or cord blood bank, please enter the code/number given to the donor by the donor registry or cord blood bank. If the donor is related, please enter the code/number by which the donor is identified in your centre. If you do not have a code for related donors, enter the family relation ("aunt", "father", etc.). *Please note that a new coding system (GRID) is being implemented and the web link to the new codes will follow.*

Number in the infusion order

For multiple donors or stem cell products, please indicate the order of infusion.

### DONRL HLA MATCH TYPE

Differences in histocompatibility (or degree of match) affect the outcome of a transplant. We define histocompatibility by looking at differences in certain proteins (or antigens) between the patient and their donor (also called "tissue typing"). The antigens which are most important in the matching procedure are the major HLA-antigens. The genes encoding these antigens are found on chromosome 6. Each individual has two copies of chromosome 6, each copy inherited from one of the parents.

#### Related donors

If the patient and their donor have the same parents and the HLA antigens are identical, it is most likely that both siblings have inherited the same copies of chromosome 6 from each parent and are therefore 'genotypically' identical, i.e. both siblings have the same genes for the HLA antigens. This is an **HLA-identical sibling** transplant. This should be made clear to you by your physician.

Occasionally other family members (parents, cousins, half siblings etc) could also be HLA-identical to the patient but could not have inherited the same copies of chromosome 6 as the patient (because they don't share the same parents). This is defined as an **HLA-matched other relative**.

Twins develop from a single egg (monozygotic) or two eggs (dizygotic). If the transplant is from a monozygotic twin, known as "identical twins" the transplant is defined as **syngeneic** and the histocompatibility genes in donor and patient are the same. However, if the donor is a dizygotic twin, the histocompatibility should be defined as for any other sibling transplants.

The donor can also be a family member (sibling, etc.) but with different HLA antigens. That would be an **HLA-mismatched related**.

#### HLA locus mismatch.

The degree of mismatch indicates how many loci have at least one mismatch. It is used as an approximation to the identification of haplotypes.

A haplotype (half of a genotype) refers to the combination of linked HLA genes transmitted on a single parental chromosome. The only way to establish whether a related donor is haploidentical is by looking at the HLA typing of the

family including parents, siblings and/or children of the patient. Usually genotypic identity can only be proven if data on both parents are available. The number of mismatches cannot be used to completely identify a family donor as haploidentical, but is a good approximation if the number of mismatches is 2 or more.

### Unrelated donors

When the donor has no family connection to the recipient it is called **unrelated donor**. These donors are found through an unrelated donor registry. For unrelated donors, more information is requested in the forms.

☐ Unrelated donor:

ION (formerly BMDW) code of the Donor Registry or Cord Blood Bank (up to 4 characters) ..... ..

WMDA / BMDW code for the Donor Registry .....

Name of donor registry or Cord Blood Bank .....

Donor centre name or code (if applicable) ..... (optional)

Donor ID given by the Donor Registry or the Cord Blood Bank listed above .....

Patient ID given by the Donor Registry or the Cord Blood Bank listed above .....

### ION code

Most existing donor registries are known universally by a unique registry code beginning ION followed by 4 digits.

The code can be found in ProMISe and the WMDA list is available on:

<https://share.wmda.info/display/WMDAREG/Database>.

This list also contains some, but not all, the Cord Blood banks. Please enter this code in the form. For reference you can find a [conversion table](#) of the ION codes and former BMDW codes in our Document Center.

### WMDA / BMDW code for the Donor Registry

Please select one of the available options (either donor registry or cord blood bank), if you do not have the ION code.

### Name of the Donor Registry

Please, enter the name of the donor registry, or, in case of cord blood, the name of the cord blood bank in full if you do not have the ION code, or the WMDA/BMDW code.

**PLEASE NOTE** that *most* countries are now centralised under one ION code (e.g.: UK are under Antony Nolan, but donations can take place under any UK donor registry), so if you know the Name of the Donor Registry, please write it in this field, after you provide the ION code.

### Donor Centre code

Some countries, e.g. Germany, have branches within the national Donor Registry. These are known as Donor Centres.

After you provide the ION code for the national Donor Registry, you will be asked to select the individual Donor Centre code from the available options

### Donor Centre name

Enter text for the Donor centre if you do not know the Donor Centre code.

### Eurocord code

In addition, Eurocord keeps a list of Cord Blood Banks. If you know the code given by Eurocord, please use it.

### Identification of Donor and Patient in the Donor Registry or Cord Blood Bank

It has become increasingly important from the clinical and the legal point of view, to be able to use joint information for the patient and donor(s) pair for each transplant. For this reason, it is very important that, while keeping anonymity, the donor data can be traced. This can only be done if the unique identification codes for the donors are stored.

It is for this reason that the EBMT is requesting the donor code given by the centre, the donor registry and the cord blood bank, together with the patient IDs these institutions give to the recipient. Although, this may look a bit exaggerated, it cannot be stressed enough how important it is to be able to identify the correct set of data and in the current situation, where there are no agreements on how to uniquely identify donors, it is best practice to collect all possible unique identifications.

Patient ID given by the Donor Registry or the Cord Blood Bank (added in 2016)

It is an Identification given by the Donor Registry or the Cord Blood Bank to the recipient. Although, this is currently an optional field, it is extremely important information, which helps in identifying the correct set of data. It is always the best practice to collect all possible unique identifications.

**NOTE:** The CIBMTR and NMDP have requested that the donor ID given by the registry, which we store in the field "*Identification of donor given by donor registry*" be entered as a number only, but retaining the leading zero if it exists. Please do not enter dashes between numbers, nor add "NMDP" or other characters to the beginning of the donor id, and do not drop leading zeroes.

We provide some examples as illustration:

As it is now	As it should be	
0257-8376-2	025783762	No dashes between numbers
NMDP0323-4119-0	032341190	No additional characters, no dashes between numbers
81706343	081706343	Keep leading 0's
US033941345	033941345	No additional characters
0699-30685	069930685	No dashes between numbers

The reason for this is to facilitate the identification of the donor when EBMT forwards the data to the CIBMTR for those centres that have requested it and ensure data integrity.

#### Donor Identification: Cord Blood

In addition to the ID for Donor Registries, we have a specific ID field for Cord Blood banks. "*Identification of the CBU given by the cord blood bank*". Note that this field is be used exclusively for the identification of cord blood units. Please only fill for Cord Blood. The navigation in Promise should skip this field for other sources of cells (BM, PB). If you notice any problems please contact the EBMT Registry Helpdesk.

#### Histocompatibility

The definition of histocompatibility in unrelated individuals has become increasingly complex since the development of more sophisticated methods of identifying the HLA-antigens. These antigens are known as A, B, C, DRB1, DQB1 and DPB1.

In simple terms, the tests can be defined as low resolution or high resolution. In the past we used low resolution typing and at this level it was possible to find HLA-identical matches for many of our patients. With increasing use of high resolution typing it is less likely that an exact HLA-match can be identified. Because this issue is so complex but may have important implications for transplant outcome, detailed histocompatibility is very important.

The number of mismatches indicates the level of difference between the donor and the patient. The number of mismatches can go from 0 (identical for that HLA type) to 2 (both copies are different between the patient and the donor).

NOTE: You do not need to submit the number of mismatches explicitly if you submit the full HLA report.

Complete number of mismatches inside each box

A B C DRB1 DQB1 DPB1







Antigenic (HLA code is 2 digits)







Allelic (HLA code is 4 digits)

0=match; 1=one mismatch; 2=2 mismatches; ND=not done  
PLEASE ATTACH LABORATORY RESULTS

For each of the HLA types, indicate the number of mismatches **detectable** using one of the two techniques: Antigenic, which has a low resolution and is also known as "by serology; 2 digit match/mismatch; broad match/mismatch"; and Allelic which has a higher resolution and is also known as "by DNA" or "molecular".

Where results for both techniques are available, they should be counted separately: count the number of antigen mismatches, then count the number of allele mismatches. An antigenic difference implies an allelic difference, so the number of allele differences can never be lower than the number of antigen differences.

Use “not done” (ND) when the specific antigen or allele has not been tested for that particular technique. If one of the techniques has not been used, put ND for all 6 entries for that technique. If there are no antigenic results, do not deduce them from the Allelic results but put “not done”.

For HLA-C the WHO nomenclature committee stopped naming antigens. C serology was abandoned and there is little evidence for any antigenicity of the new variants. C serology stops at Cw10. Therefore, for all alleles C\*12 and up there is no serological correspondence defined.

#### IMPORTANT NOTE

Regardless of whether you submit Med-A or Med-B paper forms, please always enclose a copy of the histocompatibility laboratory results. When you enter data directly in the database please ensure the HLA typing is completed. Some national registries will enter this data on your behalf, for example BSBMT Registry in the UK.

A [manual on HLA data entry](#) is available to download

#### ABODON

#### BLOOD GROUP, DATE OF BIRTH AND SEX OF DONOR

Indicate the blood group of the patient and the Rh factor status.

#### DATDONBD

Please fill in the date of birth of the donor (or his/her age)

#### DONSEX

The sex of the donor, which you may find in the histocompatibility forms, is important in relation to GvHD (graft *versus* host disease).

#### VHIVDON

**SEROLOGIC STATUS OF THE DONOR** (please see “ANTIBODIES/ANTIGENS” in the [patient](#), page 111)

#### ETC

HIV and/or HBV positivity are reasons to search for another donor. **CMV** is very important.

#### Date of harvest or cord blood collection

Indicate the date the cells were collected from the donor.

#### VCYTOKDN

#### GROWTH FACTORS ADMINISTERED TO THE DONOR

Growth factors (cytokines) are given to the donor for the collection of stem cells from the peripheral blood. They can also be used prior to the collection of bone marrow but this is less common.

#### VCYTOSD

Growth factor (= in most cases G-CSF or GM-CSF)

If administered, write the name of the growth factor in the space provided. Otherwise, tick No.

#### DID THIS DONOR PROVIDE MORE THAN ONE STEM CELL PRODUCT?

Indicate whether the donor provided more than one stem cell product.

If one product only e.g. PB, answer No and fill in details on "Donor 1" - "Product Number 1". (This includes one product given over several days, for example due to a low yield of cells during collection. Count the first day of infusion as day 0 and note the total cumulative cell counts).

If more than one product from the same Donor e.g. BM and PB, please fill "Donor 1" - "Product 1 AND 2"

#### SOURCE OF STEM CELLS FOR THIS PRODUCT

#### STEMCEDO1

Bone marrow  
Peripheral blood  
Cord blood

## GRAFT MANIPULATION

Graft versus host disease (GvHD) is caused by T-lymphocytes present in the donor stem cell graft (blood or bone marrow). It can be prevented by removal of the T-lymphocytes prior to the infusion of the cells. This may be done either

by specifically removing the T-cells (using a monoclonal antibody or a method which detects the cells by some difference in their physical properties e.g. size, density etc), or by positively selecting stem cells (again by using an antibody, usually to CD34 or AC133) thereby leaving the T-cells behind. Not all transplant centres practice T-cell depletion because despite the beneficial effects in the prevention of GvHD, it is also associated with an increased risk of disease recurrence.

#### EXVIMANI **GRAFT MANIPULATION EX-VIVO (INCLUDING T-CELL DEPLETION)**

*Ex-vivo* (same as *in vitro*) manipulation means “treatment of the graft in the laboratory”. Sometimes the graft is treated to remove plasma and/or red cells to try to prevent major ABO incompatibility reactions, but these manipulations are not considered under this question.

Report only manipulations performed at the transplant centre. If the cells, particularly, cord blood cells have been manipulated before reaching the transplant centre, these manipulations should not be reported here.

**VNEGSELE Negative:** T-lymphocytes (= T-cells), B-lymphocytes or NK-cells may be depleted from the graft. For example by elutriation or the addition of monoclonal antibodies (CD3 or CD52 (Campath)). The selected cells are discarded from the graft.

NOTE: Campath is sometimes added to the bag containing the cells, and gets infused to the patient together with these same cells during the transplantation. This treatment is known as “Campath in the bag”. In this case, the difference between *ex vivo* and *in vivo* treatment is blurred. To avoid double reporting of the same treatment, we advise that, until further notice, “Campath in the bag” is not reported here. Please, see **GVHD PREVENTION IN THE RECIPIENT**, below.

**VPOSITSE Positive:** Selection of stem cells for example by the monoclonal antibody CD34. The selected cells are used as graft.

**VEXPANSI Expansion:** This is a technique currently under evaluation to increase the number of collected cells in the laboratory. This is a very experimental procedure and only preliminary results have been reported to date.

**GENEMANI Gene manipulation:** This is a procedure by which techniques of gene transfer/transduction are used to alter the structure and characteristics of genes in the graft before the cell infusion. This is a very experimental procedure which is used in cases of inborn errors.

## CELL INFUSION

#### INFUSRT **CELL INFUSION METHOD AND CELL VIABILITY**

The use of cryopreserved stem cells was commonplace in autologous transplantation. Now, there may be good reasons to cryopreserve stem cells in allogeneic transplant. For instance, if a large number of stem cells are required e.g. for a haploidentical transplant or for a non myeloablative allograft, it may be necessary to collect cells from the donor on two separate occasions.

Cryopreservation is, of course, essential in Cord blood banks and, for the time being, the infusion method and the cell viability need only be reported for cord blood.

#### **CELL INFUSED**

Cell counts may be performed on the stem cell product at various time points and sometimes it is difficult to decide which should be reported as the “cells infused”. First, a count may be done immediately after collection. If the stem cells are infused directly into the patient this would also be the number of ‘cells infused’. If the stem cells are manipulated in the laboratory in any way, e.g. removal of red cells or plasma because of ABO incompatibility; or cells are selected for sub-populations such as CD34+ cells, then the count will be repeated after completion of the manipulation. If the cells were then infused into the recipient this would then be the number of ‘cells infused’. If the cells were cryopreserved it is possible that some of the cells might be lost during the process of freezing. At the time of thawing a further count would be performed and then this would be the number of ‘cells infused’.

However, when cryopreserved cells are thawed they often have to be given immediately to the patient and it is not always possible to obtain an accurate count. Ask your physician for the procedure in your own laboratory. If you cannot provide a

count that accurately reflects the number of 'cells infused' then record the count you have available but make a note of the particular circumstances.

#### Total number of cells actually infused

Total number of nucleated cells, CD34+, and T-cells after thawing and manipulation (if either or both occurred).

Nucleated cells	<b>INFNUC</b>	consist of: all cells, minus erythrocytes
CD34+ cells	<b>INF34PC</b>	are: an immunological description of stem cells.
T-cells	<b>TCELLS</b>	are: an immunological description of T lymphocytes.

Make sure to report the numbers in the appropriate column (ie. bone marrow, peripheral blood, cord blood). Note that the units change according to type of cell and type of source.

Please note that these numbers of cells have to be reported in number per kg body weight of the recipient.

## HSC TRANSPLANTATION

### BMTNR

#### Chronological number of HSCT for this patient

This item is very important. It refers to the number of the transplant, whether allogeneic or autologous, that this patient has received throughout his/her lifetime, regardless of whether the previous transplants have been performed in your centre or in other centres. It is NOT the serial number of this transplant within all the transplants performed in your centre; and it is NOT the number of the transplant that this patient has received in your centre only.

If this is not the first transplant for this patient, please indicate the date and type of the previous transplant.

If this is not the first allograft for this patient, please indicate if the same donor is being used.

If the patient has received a transplant in another institution, please indicate the centre's CIC if known. If not known, write down the name of the institution and its city.

### VMULGRAF

#### HSCT part of a multiple sequential graft protocol:

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 (*reduced 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.

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 (ie: relapse) should not be considered part of a multiple transplant program.

## PREPARATIVE TREATMENT (*conditioning*)

### VCONDITI

#### PREPARATIVE (CONDITIONING) REGIMEN GIVEN

Yes (most cases) usually chemotherapy with or without TBI.

No, for instance for some inborn errors.

## MYELABR

If Yes, **Was regimen intended to be myeloablative?** (*allo only*) ("*mini allo*", "*reduced intensity*")

The conventional HSCT was always myeloablative, understanding by this: ablation of the marrow with pancytopenia which could last for over a month, required SCT for marrow recovery, and producing complete donor chimaerism. If these conditions are met, answer "Yes".

Recently, several groups have tried to reduce the toxicity associated with transplants by reducing the doses of chemotherapy and/or radiotherapy given in the conditioning regimen. There are many different reduced intensity conditioning protocols and the intensity of the chemo-radiotherapy can vary from levels very close to conventional conditioning to regimens based only on immunosuppression. However, not all reduced intensity protocols are non myeloablative. The following guidelines should be followed to determine whether a regimen is truly non myeloablative in which case the answer to this question should be "No":

Any regimen with 50% or less equivalence to a standard conditioning regimen is considered non myeloablative. This includes not only the 50% reduction of the total dose of a given drug (or TBI), but also the use of a single drug in a standard dose but without other drugs (or TBI) usually included in the standard protocol.

The standard conditioning regimens vary according to the disease, so the non myeloablative regimens will also vary. The addition of ATG or any mono or polyclonal antilymphocyte antibody or the addition of purine analogues does not change the intensity category.

In Appendix III (page 149) we list established regimens for selected diseases. The above definition can be applied also to published protocols not included in the tables below.

Common reasons for a non myeloablative regimen are recipient age, co-morbid conditions, etc. Tick only one of them as the **Main reason**.

In some cases, especially in patients with MDS and blasts in the bone marrow, or in patients with refractory or non complete remission prior to an allograft, it is becoming increasingly common to use AML like therapy followed immediately (usually after 3 days) by mainly reduced conditioning regimen... (e.g FLAMSA regimen...). In those cases the AML like therapy should be reported as part of the preparative regimen (conditioning).

**Please note** that for cases where the Conditioning was started, but was stopped before it was complete, due to health reasons, and the HSCT was not performed, but the patient is still Alive, the whole of the information needs to be reported, regardless of the fact that there was no HSCT performed. Please contact the Registry Helpdesk ([registryhelpdesk@ebmt.org](mailto:registryhelpdesk@ebmt.org)) for more information and guidance. The same stands for the case that the Conditioning was complete, but the HSCT still did not take place. For more information, Please see page 13 **TYPE OF HSCT**

## VCHEMOTH

Drugs (*agents*)

[RETURN TO AUTOGRAFT](#)

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). If collecting data retrospectively and drugs were stopped due to adverse events or early death, please still register the drugs which were *intended* to be given. With respect to MoAB, only indicate those infused directly into the patient before administration of the graft and not MoAB used *ex vivo* for graft manipulation. Any drugs, MoAB, etc. administered after the graft should not be entered here.

Unfortunately, the same drug may have several different names depending on the country or product. Before deciding that the drug is not listed, consult the existing drug list ([LIST OF DRUG NAMES & SYNONYMS](#)) on the EBMT website

This document provides alternative names for many of the drugs.

Only use **Other** when you are absolutely sure the drug is not listed. In this last case, write the name of the drug clearly; do not use abbreviations.

Indicate the prescribed dose and the units in which the dose is given for each agent. Do not provide daily or weekly doses, but the **final cumulative** dose received by the time the regimen has ended. For example, if the dose of a particular drug is 100 mg/m<sup>2</sup> on days 1 and 2, then 100 mg/m<sup>2</sup> x 2 days=200 mg/m<sup>2</sup> and the dose to be entered should be **200 mg/m<sup>2</sup>**.

The units listed are those most commonly used. If the units used in your centre are different, please try to convert the dose as necessary to one of the listed units. If this is not possible, write on the margin the name of the units used.

In some disease, like lymphomas, some active drugs or radioactive compounds have been linked to a monoclonal antibody capable of binding malignant cells. The aim of this technique is to use the monoclonal antibody to pursue an “intelligent” treatment, carrying the drug linked to the antibody to the malignant cells, and only to them. It has been used to date for some cases of lymphomas.

For this reason, if the agent being reported is a monoclonal antibody (MoAB), indicate whether it is radiolabelled (the molecule contains a radioactive isotope). If the answer is "Yes", the doses to be used are the ones under UNITS IF RADIOLABELLED MOAB. Again, it should be reported as **final cumulative** dose.

Note that additional information is required if you are reporting the use of

- busulphan: route of administration ☐ Oral ☐ IV ☐ Both

- ATG and ALG (antithymocyte/antilymphocyte globulin antibodies). These are extracted from the serum of horses or rabbits immunised with T-cells. Indicate the Animal origin.

**VRADICON** TBI (total body irradiation): if present, almost always associated to chemo. Indicate the total dose in Gy, for instance; 2 days of 6Gy each → total dose is 12 Gy. To transform cGy into Gy, multiply by 100.

**VNUMFRAC** Number of fractions

For more information on TBI, please refer to the TBI section in this manual. Total Body Irradiation, page 142)

**VTLICON** TLI , TNI, TAI

Total lymphoid irradiation (TLI), total node irradiation (TNI) or total abdominal irradiation (TAI) is sometimes used to further immunosuppress the patient in order to facilitate engraftment. Typically the field of irradiation in TLI would include most sites of lymphoid tissue, such as spleen, liver and lymph nodes above and below the diaphragm.

**VLCRACON** Local radiotherapy

[{Return to Autograft}](#)

Refers to radiotherapy given to sites of definite or possible residual disease. Sometimes, patients with acute lymphoblastic leukaemia or lymphoblastic lymphoma are given additional irradiation to the central nervous system to prevent local relapse. Should be registered as conditioning only if it happens before the cell infusion. Otherwise, it should be registered as additional therapy post HSCT.

## TREATMENT DURING THE IMMEDIATE OR AROUND THE POST-TRANSPLANT PERIOD

**VGRWFACT** **GROWTH FACTORS**

Cytokines or growth factors e.g. G-CSF, GM-CSF, SCF, IL-11 may be deliberately given (as part of a planned protocol) after the graft to facilitate engraftment. Please record such use of cytokines here and write the name of the cytokine in the space provided. Indicate first date cytokine given.

Cytokines given for engraftment failure (usually after approximately three/four weeks) should be reported under the topic “TREATMENT FOR FAILURE”

**VADDTREA** **CELLULAR THERAPY**

Indicate if the patient had cell infusions for the original condition just before or after the HSCT. In some cases, DLI are given as part of the transplant protocol. These infusions are usually given after the transplant but sometimes can be given before the transplant.

In other cases, the cell infusions are given to treat the original disease if the response is not complete, or for complications derived from the transplant.

**VADCELLT** Cell infusion (CI):  
☐ Lymphocyte      ☐ Mesenchymal      ☐ Fibroblasts .....

If additional cell infusion is given, indicate the date of the first infusion which can be the same as the date of the transplant. Cells such as lymphocytes, mesenchymal, dendritic, etc. could be given to improve chimaerism or solve GvHD complications. Note that TCL stands for T-cell lymphocytes and should be reported as a DLI (donor lymphocyte infusion).

Indicate the reason for any treatment.

☐ Planned/protocol should be used when this particular treatment forms part of the overall protocol involving the HSCT and had been decided upon before the HSCT procedure was started.

All other reasons refer to decisions made *a posteriori* after assessing the patient after the transplant.

Number of infusions within 10 weeks .....

Cell infusion treatment is often given as sequential cell infusions through a series of days or even weeks. In order to make the data comparable, one episode of cell infusion treatment (one “CI”) is defined as any number of cell infusions that take place for the same indication within 10 weeks from first to last infusion.

If the indication for the treatment changes within the 10 weeks, that would be considered as 2 separate episodes of cell infusion (2 “CI”), with the 2<sup>nd</sup> episode starting on the 1<sup>st</sup> day infusions were given after the change in indication.

#### **VAGVHDP** **GvHD PREVENTION IN THE RECIPIENT (THERAPEUTIC IMMUNOSUPPRESSION)**

This is immunosuppressive treatment that is given to the patient in a prophylactic manner to prevent the development of GvHD. If collecting data retrospectively, please specify the drugs which were *intended* to be given.

Patients receiving syngeneic transplants do not receive this treatment.

**VAGVHDP8** Most of the time, the **Immunosuppressive chemotherapy** includes cyclosporin and methotrexate. Cyclosporin may also be given alone. More recently newer agents are being used for the prevention of GvHD e.g. FK506 (Tacrolimus), mycophenolate mofetil, monoclonal antibodies such as Campath. If “Campath in the bag” (see **GRAFT MANIPULATION EX-VIVO**), report it here.

Unfortunately, the same drug may have several different names depending on the country or brand. Before deciding that the drug is not listed, consult the existing drug lists to look at other names. Only use **Other** when you are absolutely sure the drug is not listed. In this last case, write the name of the drug clearly; do not use abbreviations.

**Extracorporeal photopheresis** is a treatment currently being used to prevent GvHD which does not involve the use of drugs.

In the case of T-cell depleted transplants, there may be no additional therapy to prevent GvHD. Do not report therapy given after the development of aGvHD. This should be reported under Treatment for aGvHD, page 125.

**VAGVHDP8** Please note that for unrelated donors and mismatched related transplantations, ALG/ATG and/or corticosteroids (DAF) may be given *before* transplantation. This is immunosuppressive therapy to facilitate engraftment and forms part of the preparative regimen (page 120): they should *not* be mentioned here.

## ENGRAFTMENT

#### **ENGNEUT** **GRAFT PERFORMANCE**

Engraftment looks at the normalisation of peripheral cell counts. In an allograft means that the stem cells of the donor have been taken up by the patient’s bone marrow (“have engrafted”). The first sign is an increase of neutrophils and we collect information on neutrophils and platelets separately.

**Haemopoietic recovery**

The dates of haematopoietic recovery are the first of 3 consecutive values in which the laboratory results indicate that the number of cells has reached the limit described below for each cell type.

**Absolute neutrophil count (ANC) recovery**

Recovery is considered to take place when the number of neutrophils in the patient's peripheral blood rises to at least  $0.5 \times 10^9/\text{litre}$  before additional treatment to obtain grafting is given. This is the absolute neutrophil count (ANC). Please note this is regardless of the use of G-CSF.

**DATRCGR2** Date Neutrophils  $\geq 0.5 \times 10^9/\text{L}$

The date to be entered is the first of the days in which the 3 consecutive neutrophil counts above  $0.5 \times 10^9/\text{litre}$  were recorded. This date must be at least 7 days after the last transfusion containing neutrophils.

If neutrophils never went below this level please report as *Never below*. This may happen in non myeloablative transplants.

You have to answer *No* to the recovery question if:

- An **autologous reconstitution** has taken place – particularly in a **RIC** (Reduced Intensity Conditioning) setting – where the Donor Cell Origin needs to be confirmed. (applicable in an allograft setting only)
- The Stem Cell source is either **PB** or **BM** and the ANC  $< 0.5 \times 10^9/\text{L}$  by **Day +28**. (applicable both in an allograft and in an autograft setting)
- The Stem Cell source is **CB** and the ANC  $< 0.5 \times 10^9/\text{L}$  by **Day +42**. (applicable both in an allograft and in an autograft setting)

**DPLAT50** Date Platelets  $\geq 50 \times 10^9/\text{L}$

**VPLAT20** Date Platelets  $\geq 20 \times 10^9/\text{L}$

The date is the first of 3 consecutive values of increasing platelet counts. This date must be at least 7 days after the last platelet transfusion.

**VPLAT20A** *Never below* indicates the number of cells of that type never went below the limit. This can happen in non-myeloablative allografts

If within 100 days after transplant the number of platelets never reached the limits indicated above, answer “**No**” to the recovery question.

**VLSTPLTT** Date last platelet transfusion : This would be the last date the patient received a platelet infusion within the 100 day period.

**Early graft loss:** This happens if neutrophils increase to  $\geq 0.5 \times 10^9/\text{L}$  for at least three consecutive values and subsequently decrease to a low level until additional treatment to obtain engraftment is given. Note that sometimes neutrophils can temporarily decrease to  $< 0.5 \times 10^9/\text{L}$  (due to viral infections, medication or GvHD) and can return to  $\geq 0.5 \times 10^9/\text{L}$  on recovery.

In allografts, there can be graft loss with normal blood levels due to autologous reconstitution. A chimaerism test (see Haemopoietic Chimaerism below) can determine whether or not there has been a graft loss. If the test has not been done, please answer “not evaluated”.

Ask your physician for the date of lost graft

**CHMPB HAEMOPOIETIC CHIMAERISM**

A “chimaera” is a creature from Greek mythology whose body is made of parts from different animals. In allogeneic transplantation the term is normally used to describe the status of donor marrow in the patient.

In the context of non myeloablative allografting, some investigators study chimaerism in the peripheral blood. In this situation it is commonplace to study the chimeric status of different sub-populations of cells e.g. lymphocytes, myeloid cells etc.

Several chimeric situations can occur;

Full (complete), 95% BM cells are from donor origin

Mixed or Partial, BM cells are both from donor AND recipient

Autologous reconstitution (no chimaerism), all the BM cells are derived from the recipient

Aplasia, no cells at all, empty bone marrow.

Indicate always the date of the test. Indicate also the identification of the donor/CBU and the number in the infusion order if multiple donors. Depending on the disease and type of allograft, several tests may be indicated using different cell types and/or methods.

Cell type on which test was performed

The cell types refer to the type of cells that are actually being identified as belonging to the donor or to the patient. The level of chimaerism may differ across cell types. Indicate the percentage of donor cells for each cell type if it has been measured.

Test(s) most commonly used are: FISH, Molecular, Cytogenetics (conventional, not FISH) and/or ABO group

**CHIMFISH** FISH (Fluorescent In Situ Hybridization)

This is a cytogenetic method that analyses non dividing cells.

**CHIMMOL** Molecular

With VNTR (variable number of tandem repeats) analyses (DNA fingerprint), the chance of finding differences between patient and donor cells is very high. Therefore this molecular technique is perhaps the first choice as a marker of chimaerism, and can be used even if the patient and their donor are of the same sex and have the same blood group.

**CHIMCYT** Cytogenetic

Pre-transplant, one or more markers of chimaerism which distinguish patient and donor are determined.

If there is a sex difference, for instance if the patient is female (XX) and the donor is male (XY), chimaerism can be easily tested post-transplant by cytogenetic analysis and/or FISH (Fluorescent In Situ Hybridization). If 95% tested cells show XY in a female patient with a male donor, then there is a full chimaerism.

**CHIMABOG** ABO Group

Another marker of chimaerism can be the blood group (for instance, patient A and donor not A, or certain other combinations). However, if the patient is O and the donor is another blood group, then it is much more difficult to determine.

In some cases, it may look like different tests provide contradictory information: full chimaerism but still a positive detection of molecular abnormalities. This is due to the difference in the sensitivity of the tests. While most tests for chimaerism can detect 1 - 5 recipient cells out of 100, BCR/ABL molecular tests, for example, can detect 1 cell out of 100,000 or even 1,000,000.

For multiple donors, not only overall but donor dependent chimaerism should be reported. That is the percentage of cells from that particular donor that are found in the patient's marrow. Fill in the table with all the instances in which chimaerism was measured, split by donor and by the cell type on which the test was performed, indicating the method. In some cases, particularly for cord blood or for certain inherited disorders, chimaerism may be tested on several dates. When this is the case, indicate the results for each **Date of test**.

NOTE: Make sure you enter the unique identification used by your centre for the donor or cord blood unit.

**TRTGRFAI** **TREATMENT FOR FAILURE**

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. 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 donor stem cells. This would be classified as a new transplant and a new set of MED-AB forms should be completed.

No specific treatment

GRFAIGR

Growth factors

GRFAITRA

Subsequent transplant (*please complete a new transplant form*)

DATOTBMT

If you report MED-B, please report on the MED-B Graft specific form the Date and type of new transplant. Then fill in a full MED-B form for this new transplant.

Autologous BM or PBSC Re-infusion

GRAFAIBM

Please report if the patient received an infusion of autologous stem cells (a top-up or boost) after graft failure. (This is not considered a transplant; you do not have to complete a new form).

GRAFAIPB

VTRENFA

Other

## ACUTE GvHD

Acute graft *versus* host disease (aGvHD) is a consequence of donor T-cells recognizing the patient's antigens as foreign. It usually consists of dermatitis, hepatitis and gastroenteritis. Although it tends to appear within the first 100 days, it can also appear later on. See page 134 for more information.

Filipovich *et al.* Biol Blood Marrow Transplant 2005; 11:945–956.

### aGvHD Manifestation

Date of onset is important. In a conventional transplant the onset of GvHD is more or less associated with the time of repopulation of the leucocytes. In T-cell depleted transplants or in non myeloablative transplants, the onset of GvHD may be delayed beyond the time of engraftment.

AGVHGRMX

Maximum grade, grade I, II, III or IV

DATAGHV

The overall grade (or the stage of skin, liver and/or gut) should be mentioned in the patients' file. If not clearly stated, ask your physician.

The maximum grade for acute graft *versus* host disease (aGvHD) is defined according to the stage presented by the skin, liver and gut. Up until 2015, there was only one stage for gut which included the symptomatology of diarrhoea, nausea and vomiting.

(Przepiorka *et al.* Bone Marrow Transplantation 1995;15: 825-828)

Currently, Gut is being subdivided into Upper gut and Lower gut as shown in the following staging table:

ORGAN		STAGE
Skin	0	No rash attributable to acute GVHD
	1	Skin rash < 25% body surface
	2	Skin rash 25-50% body surface
	3	Skin rash >50% body surface
	4	erythroderma
Liver	0	Bilirubin < 34 micromol/L
	1	Bilirubin 34-50 micromol/L
	2	Bilirubin 51-102 micromol/L
	3	Bilirubin 103-255 micromol/L
	4	Bilirubin > 255 micromol/L
Lower Gut	0	No diarrhoea attributable to acute GVHD / diarrhea ≤ 500 mL/day
	1	Diarrhoea volume 501 - 1000 ml/day
	2	Diarrhoea volume 1001 - 1500 ml/day
	3	Diarrhoea volume ≥ 1501 ml/day
	4	Severe pain with or w/o ileus
Upper Gut	0	No persistent nausea or vomiting
	1	Persistent nausea or vomiting

You should report the maximum grade seen during the relevant period being studied as calculated from the table below.

<b>grade 1:</b> Skin stage 1 or 2	AND	Liver stage 0	AND	Upper Gut stage 0	AND	Lower Gut stage 0
<b>grade 2:</b> Skin stage 3	OR	Liver stage 1	OR	Upper Gut stage 1	OR	Lower Gut stage 1
<b>grade 3:</b>		Liver stage 2 or 3	OR			Lower Gut stage 2, 3 or 4
<b>grade 4:</b> Skin stage 4	OR	Liver stage 4				

#### VGVDHRES aGvHD resolution

If the acute GvHD resolved, please mention the date on which it was thought to have resolved completely.

#### VTRAGVHD

#### VAGVHDT1

#### VPREDDOS

#### VTRAGVH2

Treatment for acute GvHD is often prednisone with or without other medication. If prednisone is given, indicate the dose. The medication list is a good place to find this information. Make sure you differentiate between medication given to prevent GvHD (prophylaxis) and that given to treat it: i.e. if cyclosporin was given as *prophylactic* medication, do not mention it here. {Return to GvHD Prophylaxis, page 121}

## COMPLICATIONS WITHIN THE FIRST 100 DAYS

#### VCOMB100 INFECTION RELATED COMPLICATIONS

If “yes” please find explanations in the “INFECTION RELATED COMPLICATIONS” section of this manual.

#### VOTCO100 NON INFECTION RELATED COMPLICATIONS

(Check all that are applicable for this period)

##### Idiopathic pneumonia syndrome

Idiopathic pneumonia syndrome (IPS) is an interstitial pneumonia occurring after stem cell transplantation for which an infectious etiology has not been identified. It is characterised by diffuse lung injury which may have numerous and possibly associated mechanisms, e.g. latent viral infection, alloreactive T-cells, cytokines, chemoradiation-induced lung injury. Usually it is detected by chest X-rays showing diffuse interstitial infiltrates. The severity varies from an asymptomatic X-ray finding to acute respiratory distress syndrome (ARDS). Diagnosis of IPS is one of exclusion of infection (particularly viral) and depends on the sensitivity of the technologies used to detect these infections.

Bronchoalveolar lavage (BAL) and lung biopsy are appropriate technologies to exclude/detect such infections in patients with an interstitial pneumonia after transplant. Other differential diagnoses include pulmonary oedema and diffuse alveolar haemorrhage (DAH).

Indicate the date of onset.

##### Veno-occlusive disease

Veno-occlusive disease (VOD) is a liver toxicity syndrome due to endothelial injury of the hepatic venules which is most likely caused by cytoreductive therapy in the conditioning regimen. VOD is characterised by jaundice, hepatomegaly and weight gain or ascites in the setting of no other liver disease. Diagnosis relies on clinical criteria, ultrasonographic findings, central venous blood pressure (>10 mm Hg) and transjugular liver biopsy. Sometimes the differential diagnosis between VOD and acute GvHD affecting the liver may be difficult. Indicate the date of onset.

##### Cataract

##### Aseptic bone necrosis

##### Haemorrhagic cystitis, non infectious

##### ARDS, non infectious

##### Multiorgan failure, non infectious

##### Transplant associated microangiopathy

##### Renal failure requiring dialysis

##### Haemolytic anaemia due to blood group

**VOTCOMPS** If other relevant complications have occurred, please describe them under Other.

## STATUS

### Med-A only

#### Best disease status (response) after HSCT

You must tick only one box. Indicate if the patient is in complete remission or not. If the patient was in CR before the transplant and is still in CR, tick Continued complete remission. Indicate the date in which the CR response was achieved or, if response was not CR, the date response was assessed

For CR definitions, please see the sections for each specific disease.

### IIDAABE **DATE OF LAST CONTACT**

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.

### GRAVHOSD **CHRONIC GRAFT VERSUS HOST DISEASE (cGvHD)**

Chronic graft *versus* host disease is most often registered with the Follow up forms. However, in rare cases cGvHD may be seen before 100 days and may be continuous from a still unresolved bout of aGvHD. See page 134 for further explanations on how to report these data.

### VRELPROG **RELAPSE OR PROGRESSION**

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. If the information is not available for a particular disease and until a more specific definition appears in the EBMT forms, a rough figure of more than 25% increase of measurable disease or the appearance of the disease at new sites may be used to define relapse/progression.

Sometimes, relapse or progression in a patient without GvHD may induce physicians to obtain a more effective graft versus tumour effect by an early reduction of the immunosuppressive drugs and/or by infusing more lymphocytes from the donor. In some other instances, the same manoeuvres are applied by physicians to patients without GvHD because they were not satisfied by tumour response: these patients should not be registered as having relapses or progressed.

## LAST DISEASE STATUS

### DISEASE PRESENCE DETECTION AT LAST CONTACT

This is the status of the disease on the date of last contact: do **not** confuse with the question above referring to Relapse or Progression.

- A patient may have relapsed after the last HSCT but still be in CR –so no disease presence detected- at last contact if they have received a successful non HSCT treatment in between.
- The opposite is also true, the patient may not have progressed but because CR was never achieved after transplant, there may be disease presence detected at last contact.

**DISCLI** Was disease detected by ..... method?:  
☐ No    ☐ Yes  
 Last date assessed ..... - ..... - .....  
☐ Not evaluated    *yyyy mm dd*

If the patient has been transplanted for leukaemia, indicate whether disease is present as detected by each of the methods (haematological, cytogenetic and molecular).

If the patient has been transplanted for other disease than leukaemia, only answer the question on clinical/haematological method. If there is any evidence that the patient is not in CR, or completely cured in the case of non malignant diseases, answer “Yes”. Note that a patient may have disease present even if they have not progressed after the transplant.

Considered disease relapse/progression: ☐ No ☐ Yes

If disease has been detected through cytogenetic or molecular methods (presence of abnormalities), please indicate whether your physician considers these abnormalities proof of relapse.

## VPATSTAT SURVIVAL STATUS

Survival status is asked at day 0, day 100 and annual follow up.

At day 0-

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. The transplant procedure is considered to start when the conditioning regimen is initiated. If the patient dies before any cell infusion is given, it should be reported on this form as option “3.Died before HSCT but after conditioning was initiated”. Otherwise, please choose from the options “1.Dead” or “2.Alive”.

At day 100-

Day 100 is when 100 days have elapsed since transplant date (day 0). If the patient dies before 100 days post transplant, it should be reported on this form as option “1.Dead”. Otherwise, please choose option “2.Alive”.

At Annual Follow up-

The options offered here are: “1.Dead”, “2.Alive” and “9.Lost to 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.

**VKARNOFS Performance score** The score may be written in the progress notes. If not, an indication of the patient's health status is probably given there. See Appendix I for scale on page 147.

## VCAUSDTH CAUSE OF DEATH

The information on cause of death is very important.

### Main

Tick only one major cause of death.

### Contributory

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.

Death can also be caused by a disease secondary to the treatment of the original diagnosis.

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.

**Main Cause of Death** (check only one main cause)

Relapse or progression

Secondary malignancy (including lymphoproliferative disease)

Transplantation related cause

**Contributory Cause of Death** (check as many as appropriate)

GvHD

Interstitial pneumonitis

Pulmonary toxicity

Infection, bacterial, viral, fungal, parasitic or other

Rejection / poor graft function

Veno-Occlusive disease

Haemorrhage

Cardiac toxicity

Central Nervous System Toxicity

Gastro Intestinal Toxicity

Skin Toxicity

Renal Failure

Multiple Organ Failure

Other

## IDENTIFICATION & SIGNATURE

It is important to collect the signature of the person responsible for filling the forms and to whom all queries should be directed. All forms should be signed.

If the information is being entered directly into the EBMT database through ProMISe, ensure the name of this person is entered under "Contact".

## ALL DISEASES

## AUTOGRAFT

This section will only incorporate those sections which are different from the AUTOgraft form. Otherwise, the user will be referred to the Allograft section.

**PERFORMANCE SCORE**

Refer to Allograft chapter for this section, page 111.

**COMORBIDITY INDEX**

Refer to Allograft chapter for this section, page 112.

## COLLECTION (harvest) OF MATERIAL ACTUALLY REINFUSED

**SOURCE OF STEM CELLS**

*Check all that apply*

**COLLECTION (HARVEST)**

VBMSC

For autograft, reinfused stem cells (SC) are obtained from the patient himself. The SC source may be either - bone marrow (BM) - for that patient, a “BM harvest or collection” has been performed in the past weeks, months or, rarely, years before the autograft; or

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.

Nowadays the most frequent option is **PB**, whereas in the past, before the ‘90s with its wider introduction of aphaeresis technologies, it was **BM**. In some cases cells from both sources can be used for the same procedure, in case one option is not enough to ensure a sufficient number of cells to reinfuse. The “Other” option is not used now for autograft.

The information requested in this section refers to the collection of cells which were subsequently re-infused. Sometimes all the cells harvested at one collection are re-infused, sometimes only part of the collection is re-infused. Please, provide information here on all collections whether they were totally or partially re-infused.

MOBDATE

Bone Marrow: Total number of collections

Indicate on how many occasions were cells collected from the patient.

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 (GF). 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 “aphaeresis”. According to the number of stem cells in the PB of each patient, a different number of sessions of aphaeresis may be needed. A “Course” is intended as one procedure starting from the mobilisation to the last aphaeresis performed. If, after one course, possibly consisting of several aphaeresis, a sufficient number of stem cells has not been obtained, the patient may be submitted to a second course. This is the information requested in the Total number of mobilisation courses field.

NMBMOB

In some rare cases (CML), cells may be collected without mobilisation.

**PERIPHERAL BLOOD MOBILISATION**

List all drugs: chemotherapy, growth factors, antibodies, etc.

For each mobilisation course, fill in:

- IDAABC** Date of 1st aphaeresis: the date of the first aphaeresis 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

**BMTNR** Chronological number of transplant for this patient

See Allograft chapter, page 118

**VMULGRAF** Transplant part of a multiple graft program

Sometimes patients are entered into protocols in which the clinician plans to perform more than one single graft at agreed intervals. If this is the case please answer “Yes” here.

If the protocol includes additional transplants but only in the event that the response to the initial transplant is unsatisfactory, this is not a multiple graft program and you should enter “No”.

**DBLAUTO** Double graft program – a program comprising of two grafts  
Planned sequential protocol – usually involving up to 4 autologous cell infusions, each preceded by high dose chemotherapy

For example, in the present for some kind of lymphomas, 2 or 3 autograft may be included in the initial protocol. Another example, mixing auto and allografts, would be the use of an autologous transplant to prepare the patients for a non myeloablative 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.

**VGRNBPR** number of this transplant \_\_\_\_\_ out of \_\_\_\_\_ pre-programmed transplants

**VSEQPROT** Please fill in the number of the transplant within the multiple graft program, and, in the case of the Planned sequential protocol, also fill in how many cell infusions the procedure consists of.

This is very important for the data manager to know whether all transplants for the procedure have been reported.

If patients have already received a transplant (autologous or allogeneic) prior to this procedure as part of earlier management, **the current transplant is not part of a multiple graft programme.**

It is unlikely that we are dealing with a multiple graft program if:

- more than 6 months/one year elapsed between two transplants;
- patient disease relapsed or progressed after the previous graft.

## EX VIVO GRAFT MANIPULATION

**EXVIMANI** **MANIPULATION**

- marrow manipulation
- PB manipulation
- both

After conventional chemotherapy, we know that residual malignant cells are still present in the patient. The complete eradication of the disease is rarely obtained, and the autograft is used with the aim to obtain a more extensive reduction and, possibly, the eradication of the disease through the administration of higher doses of

chemotherapy (“high dose treatment”). However, if the malignant cells are still present in the patient, they will also be present in the collected cells – either BM or PB, or both if that is the case. These residual cells may be responsible for the any relapse of the disease which occurs after autograft.

To reduce the risk of re-infusing tumour cells back into the patient, the collected material is manipulated *ex-vivo*. The manipulation techniques, some called “purging”, are all experimental techniques since, unfortunately, a “standard” technique, universally recognized as effective in reducing the relapse risk, is still not available.

#### **VNEGSELE Negative**

- VCYCLOST** - Malignant cells are destroyed (or removed) from the graft, either with some drug like
- VCYCLOMD** cyclophosphamide derivatives, or with specific antibodies that bind to them;
- VMOABNS**

#### **VPOSITSE Positive**

- Selection of stem cells for example by the monoclonal antibody CD34. The selected cells are used as graft.

#### **VEXPANSI Expansion**

- This is a technique currently under evaluation to increase the number of collected cells in the laboratory. This is a very experimental procedure and only preliminary results have been reported to date.

#### **GENEMANI Gene manipulation:**

- This is a procedure by which techniques of gene transfer/transduction are used to alter the structure and characteristics of genes in the graft before the cell infusion. This is a very experimental procedure which is used in cases of inborn errors.

## PREPARATIVE TREATMENT (*conditioning*) AND INFUSION

Autografts always have a preparative regimen which in most cases involve at least one drug. Please refer to this section in the "Allograft" chapter, page 119

Remember that in the case of a top-up of PBSC infusion due to graft failure, the infusion is reported in the failure section of that transplant, and not as a new transplant registration.

### CELLS COLLECTED AND INFUSED

For autograft it is necessary to cryopreserve the collected stem cells until the time when the patient will be submitted to the autograft (this may be weeks, months, rarely years after the collection). When cells are thawed, the total count will usually be reduced versus the number of cells collected.

Cell counts may be performed on the stem cell product at various time points and we request that all evaluations are reported here.

**NUCL1** Nucleated cells consist of: all cells, minus erythrocytes

**CFUGM1** CFU-GM cells are: Colony Forming Units, a functional description of stem cells.

**OTCLDS1** CD34+ cells are: an immunological description of stem cells.

#### **Evaluated before manipulation and cryopreservation:**

Numbers of counts performed immediately after the collection and before any *ex-vivo* manipulation and/or cryopreservation. These counts are always available, and sometimes they may be the only counts available.

**Evaluated after manipulation and before cryopreservation:**

If the stem cells are manipulated in the laboratory in any way (see above “**MANIPULATION**”), then the counts will be repeated after completion of the manipulation and before cryopreservation.

**Cells actually infused**

These are counts of the cells after being thawed and just prior to infusion. Unfortunately, these numbers are difficult to come by.

Make sure to report the numbers in the appropriate column (ie. bone marrow or peripheral blood). Sometimes, but rarely, a patient may have a transplantation of cells originating from both the marrow AND the peripheral blood of the donor.

Please note that these numbers of cells have to be reported in number per kg body weight of the recipient.

## TREATMENT DURING THE IMMEDIATE POST-TRANSPLANT PERIOD

Please refer to this section in the "Allograft" chapter above.

## ENGRAFTMENT

ENGNEUT

**GRAFT PERFORMANCE**

Haematopoietic recovery (*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  $0.5 \times 10^9$ /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.

For more details, refer to this section in the "Allograft" chapter above.

TRTGRAFI

**TREATMENT FOR FAILURE**

Refer to this section in the "Allograft" chapter above.

## COMPLICATIONS WITHIN THE FIRST 100 DAYS

Refer to this section in the "Allograft" chapter above.

## STATUS AT 100 DAYS

Refer to this section in the "Allograft" chapter above.

## IDENTIFICATION & SIGNATURE

Refer to this section in the "Allograft" chapter above.

## ALL DISEASES

## GENERAL FOLLOW UP

## COMPLICATIONS BEFORE/ AFTER 100 DAYS

**Date of last follow up or death**

This should be the last date the patient was known to be alive if alive. This date may be later than the last time the patient visited the clinic or was clinically assessed.

Lost to follow up

We ask that centres try to enter follow up data regularly, even if it is difficult to keep in touch with patients. However, if you have tried but completely lost contact with a patient, the last status can be recorded as “lost to follow up”. Note that the date of this last assessment should be the last date that the patient was known to be alive. It should not be the date that you decided the patient was lost to follow up.

In the registry database it is not possible for centres to enter ‘lost to follow up’ within 2 years of transplant. If you have a genuine case within this timeframe, for example the patient has gone overseas and you have lost contact, please contact [registryhelpdesk@ebmt.org](mailto:registryhelpdesk@ebmt.org) to revise the follow up status.

If a ‘lost to follow up’ patient does reappear in your centre, it will still be possible to enter a new follow up in the future.

AGVHGRMX  
GRAVHOSD

**GRAFT VERSUS HOST DISEASE**

Graft versus host disease is caused by T-lymphocytes present in the donor stem cell graft (blood or bone marrow). In the past, because aGvHD tended to happen within the first months while cGvHD tended to happen after 100 days from the HSCT, and even though their features are different, the interval between date of onset and the HSCT was the only parameter used in differentiating one from the other.

Currently, it is recognised that time should not be used to determine the type of graft *versus* host disease, and the NIH (National Institute of Health) consensus recognises the following possibilities

**NIH consensus**

1) acute GvHD (absence of features consistent with chronic GvHD ), comprising:

- classic acute GvHD (before day 100), and,
- persistent, recurrent, or late acute GvHD (after day 100, often upon withdrawal of immunosuppression);

2) chronic GvHD , comprising:

- classic chronic GvHD (no signs of acute GvHD ), and,

3) an overlap syndrome, in which features of both acute and chronic GvHD are present.

AGVHGRMX

**ACUTE GRAFT VERSUS HOST DISEASE (AGVHD)**

For the general features, go to aGvHD in Allograft, page 124.

Indicate whether the aGvHD is of new onset or comes after an earlier episode either continuously or as a recurrence.

As late or delayed aGvHD can be caused by tapering (sequential decreasing) of the immunosuppressive regimen, cell therapy, or other causes which may delay the onset such as non myeloablative conditioning, please, indicate the cause. If there are no obvious reasons for the appearance of aGvHD at this time, select “Unexplained”.

For Date of onset of this episode, indicate the date of onset for the new episode whether it is the first one or a recurrence. If the aGvHD is continuing from a previous, reported, episode, tick Not applicable.

### CHRONIC GRAFT VERSUS HOST DISEASE (cGvHD)

(*allografts only*)

#### GRAVHOSD

#### Onset of cGvHD

Mark; "No (*never*)" if the patient has never yet had an episode of cGvHD.

1) If the patient has had only one episode of cGvHD, mark "Yes" and then "First episode". Indicate the date of onset of cGvHD for this episode. If the onset of cGvHD is seen when aGvHD has still not been resolved and its therapy has not been completed, it should be considered as a "First episode" and should have its own date as separate to the aGvHD onset date.

2) If the patient has had GvHD occurring, after resolution of a previous chronic GvHD episode, mark "Yes" and then "Recurrence". Indicate the date of onset of cGvHD for this recurrence.

Resolved since last report (*currently absent*)

For both, 1) and 2) above, indicate whether the episode has resolved by the date of last contact.

3) If the GvHD episode reported in the last follow up is still present, mark "Yes" and then "Continuous since last reported episode".

#### Maximum grade

In all cases in which there has been or is GvHD, please mark the grade, 'limited' or 'extensive; this information should be in the patient's file or ask your physician. cGvHD is considered limited if it is present only in the liver and/or a localised area of the skin. If the cGvHD affects any other organ(s) or there is generalised skin involvement, it is considered to be extensive. Tick only one box.

#### Maximum NIH consensus score

The NIH scoring system was first published in 2005 and has since been validated several times. As described in [http://www.bbmt.org/article/S1083-8791\(14\)01378-0/pdf](http://www.bbmt.org/article/S1083-8791(14)01378-0/pdf), eight organs or sites (skin, mouth, eyes, gastrointestinal tract, liver, lungs, joint and fascia, and genital tract) are considered for calculating global score. Elements included in the proposed global scoring include both the number of organs or sites involved and the severity score within each affected organ.

The scoring is complex and needs to be recorded by the physician. The quoted publication contains an extensive description of the necessary measurements to obtain the score. Indicate the maximum NIH score during this period, as per the results of these measurements.

#### Evolution

It is important to report if chronic GvHD followed acute GvHD or if chronic GvHD is a de novo GvHD. If cGvHD follows from a non resolved aGvHD, put date of onset as 100 days +1.

#### cGvHD resolution

#### CGVHDRES

Please check the previous follow-up form and mark whether the chronic GvHD resolved (PLUS date), whether this was previously reported, whether it didn't resolve yet or whether this issue is not applicable (there was never cGvHD).

#### DRESCGVH

The day that the GvHD medication was stopped is NOT necessarily the resolution date. Resolution should be determined after clinical investigation and will be mentioned in the patient's file.

#### VCOMA100

### INFECTION RELATED COMPLICATIONS

If "yes" please find explanations in the "INFECTION RELATED COMPLICATIONS" section of this manual.

**VOTCO100** **NON INFECTION RELATED COMPLICATIONS**  
**IDAABECA** (Check all that are applicable for this period)

For Idiopathic pneumonia syndrome, VOD, EBV lymphoproliferative disease, see question under the "ALLOGRAFT" section of this manual, above.

**Cataract**

Cataract, is an alteration in the lens as a consequence of irradiation or steroid therapy. Usually -if the cataract is severe- the lens is removed by surgery

**Aseptic bone necrosis**

Aseptic bone necrosis, is referring to bone necrosis in the hip appearing months or years after transplant. Possible causes are steroids or irradiation.

Haemorrhagic cystitis, non infectious

ARDS, non infectious

Multiorgan failure, non infectious

Transplant associated microangiopathy

Renal failure requiring dialysis

Haemolytic anaemia due to blood group

**VOTCOMPS** If other relevant complications have occurred, please describe them under Other.

**LGRAFTL** **GRAFT ASSESSMENT AND HAEMOPOIETIC CHIMAERISM**  
**Late graft failure**

**CHMPB** If there is no chimaerism (<5%) or persistent neutropenia or both on assessment this indicates a late graft failure. Indicate whether this is due to Aplasia (lack of cells in marrow) or to Autologous reconstitution (most cells of patient origin).

**VADDTREA** **CELLULAR THERAPY**

Indicate if the patient had additional treatment for the original condition or complications derived from the transplant.

**VADCELLT** Cell infusion (CI):

- ☐ Lymphocyte      ☐ Mesenchymal      ☐ Fibroblasts  
☐ Dendritic cells      ☐ Other, specify .....

If additional cell infusion is given, indicate the date of the first infusion which can be the same as the date of the transplant. Cells such as lymphocytes, mesenchymal, dendritic, etc. could be given to improve chimaerism or solve GvHD complications.

Indicate the reason for any treatment.

☐ Planned/protocol should be used when this particular treatment forms part of the overall protocol involving the HSCT and had been decided upon before the HSCT procedure was started.

All other reasons refer to decisions made *a posteriori* after assessing the patient after the transplant.

Number of infusions within 10 weeks .....

Cell infusion treatment is often given as sequential cell infusions through a series of days or even weeks. In order to make the data comparable, one episode of cell infusion treatment (one "CI") is defined as any number of cell infusions that take place for the same indication within 10 weeks from first to last infusion.

If the indication for the treatment changes within the 10 weeks, that would be considered as 2 separate episodes of cell infusion (2 "CI"), with the 2<sup>nd</sup> episode starting on the 1<sup>st</sup> day infusions were given after the change in indication.

#### **Disease treatment** (*apart from cell infusion*)

Indicate if the patient had any other type of treatment (radiotherapy, etc.) and whether it was Planned or Not planned, that is, decided upon after assessing the patient after the transplant.

#### **VRELPROG**

#### **RELAPSE OR PROGRESSION AFTER TRANSPLANT**

For explanations regarding this issue, please check the disease specific sections of this manual and the same question under the "ALLOGRAFT" section of this manual, above.

#### **LAST DISEASE STATUS**

##### **DISEASE PRESENCE/DETECTION AT LAST CONTACT**

#### **DISCLI**

Was disease detected by ..... method?:

☐ No ☐ Yes

Last date assessed ..... - ..... - .....

☐ Not evaluated      *yyyy mm dd*

If the patient has been transplanted for leukaemia, indicate whether disease is present as detected by each of the methods (haematological, cytogenetic and molecular).

Considered disease relapse/progression: ☐ No ☐ Yes

If disease has been detected through cytogenetic or molecular methods (presence of abnormalities), please indicate whether your physician considers these abnormalities proof of relapse.

Cytogenetic and molecular methods are more sensitive than haematological methods. The appearance of molecular or cytogenetic disease in the presence of a haematological CR is the "minimal residual disease" which can also be detected by other methods, like flow cytometry. It is possible to detect cytogenetic or molecular disease in the absence of haematological relapse.

Flow Cytometry will be added as a separate category in the near future. In the meantime please include Flow Cytometry tests in the clinical/haematological category

If the patient has been transplanted for other disease than leukaemia, only answer the question on clinical/haematological method. If there is any evidence that the patient is not in CR, or completely cured in the case of non malignant diseases, answer "Yes". Note that a patient may have disease present even if they have not progressed after the transplant.

#### **SECONDARY MALIGNANCY, LYMPHOPROLIFERATIVE OR MYELOPROLIFERATIVE DISORDER DIAGNOSED**

#### **IDAABB**

Patients can develop secondary disorders. If this is the case, tick "Yes", provide date of diagnosis and indicate which diagnosis. This can be any malignant disease for which the patient had not been diagnosed before the transplant. (If a patient has MDS that transforms to AML post transplant, the AML is considered as a secondary malignancy).

#### **DISMCLFD**

Among these secondary diseases, EBV lymphoproliferative disease (EBV-LPD) can happen after transplant, and is also known as Post-transplant lymphoproliferative disease (PLT). It may be associated to EBV infection.

The majority of adults are infected by the Epstein-Barr virus (EBV), the agent of Infectious Mononucleosis. In a normal individual, the EBV can drive a B-lymphocyte proliferation, which is

controlled by specific clones of T-lymphocytes. When such T-lymphocytes are lacking, the growth of B-lymphocytes can be so extensive to induce an accumulation of B-lymphocytes in the peripheral blood, the lymphoid organs, and extralymphatic tissues. The clinical features are those of a lymphoid tumour mimicking an aggressive malignant lymphoma (ie. lymphocytosis, enlargement of lymph nodes/spleen/liver, involvement of the central nervous system, fever, etc.). The highest risk of EBV-LPD is when the donor T-lymphocytes are not transfused with the graft (ie. in T-cell depleted transplants) in unrelated HLA mismatched transplants, but the complication may still occur at lower frequencies in other types of transplants. The diagnosis relies on histological examination of affected tissues. Indicate the date of onset.

**VCONCEPT PREGNANCY AFTER HSCT**

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. (This includes all types of conception: natural and assisted). Indicate also whether the pregnancy resulted in a live birth.

**VPATSTAT DEATH**

See same question under the “ALLOGRAFT” section of this manual, page 127.

**ALL DISEASES**
**INFECTIOUS COMPLICATIONS**
**COMPLICATIONS WITHIN THE FIRST 100 DAYS**
**COMPLICATIONS AFTER 100 DAYS**
**INFECTION RELATED COMPLICATIONS**
**VCOMB100**

- ☐ No complications  
☐ Yes

The Infectious Diseases Working Party (IDWP) has published on the web the document “[Definitions of Infectious Diseases and Complications after Stem Cell Transplant](#). A proposal from the Infectious Diseases Working Party of the EBMT” which should be consulted before filling in these sections of the MED-B forms.

(Check all that are applicable for this period)

Type		DATE
<b>INFECTIO</b>	Use the list of pathogens in next page for guidance. Use “ <i>unknown</i> ” if necessary.	PROVIDE DIFFERENT DATES FOR DIFFERENT EPISODES OF THE SAME COMPLICATION IF APPLICABLE. <b>IDAABE / BEGINFEP</b>
Bacteraemia/fungemia/viremia	<b>PATHOGEN</b>	

Each infectious episode should be ticked or specified under TYPE, in the first column. For each episode, a pathogen should be identified (a list of likely pathogens is listed in the MED-B forms). How to define each episode and rules on identification of the pathogens are provided in the Appendix mentioned above. If the specific episode cannot be found among those listed, please specify it under other. Each episode must be accompanied by the date it was first diagnosed on the right hand column.

## ALL DISEASES

## DONOR LYMPHOCYTE INFUSION

## PATIENT

The successful use of donor lymphocyte infusions (DLI) for the treatment of recurrent leukaemia after allogeneic transplantation was first shown in patients with recurrent chronic myelogenous leukaemia (CML). Between 70 % and 80% of patients with relapse and without signs of transformation respond to DLI with a complete cytogenetic remission. The stage of the disease at the time of transplantation, i.e. chronic phase, accelerated phase or blastic phase is even more relevant in predicting the response to DLI.

**INDICATION**

The most frequent indication for the treatment with DLI is relapse of leukaemia. Other indications may be pre-emptive treatment in cases of a high risk of relapse, the conversion of a mixed chimaerism into a complete chimaerism either as correlate of an impending relapse or possible rejection. In some patients there is a poor marrow function due to residual host versus graft activity with a risk of rejection or persistent viral infections interfering with hematopoiesis. This would also be an indication for DLI.

The indication for DLI cannot be stated without consideration of the condition of the patient.

**Relapse / progression**

Relapse is defined as the reappearance of the leukaemia or the tumour after a remission. This remission can have been a complete remission or only a partial remission. In a wider sense also persistence of leukaemia or tumour may be included in the definition for the purposes of DLI treatment.

Definitions of molecular and cytogenetic relapse are only valid if immunosuppression as prophylaxis for Graft-versus-host disease (GvHD) has been discontinued for at least 30 days.

The relapse definitions below relate to Chronic Myeloid Leukaemia (CML). If you are filling in the DLI form for a disease other than CML please refer to the relevant disease section in this manual.

☐ **molecular relapse**

Presence of cells with the BCR/ABL fusion protein by an assay with a sensitivity to allow detection of 1 t(9;22) positive cell in  $10^5$  to  $10^6$  cells in a patient lacking any other evidence of the disease (ie. haematological remission and cytogenetic CR). Results must be confirmed >30 and <90 days after the 1<sup>st</sup> positive assay unless any change in current therapy was performed because of the 1<sup>st</sup> positive assay. Cytogenetic CR and haematological CR must also be confirmed at second assay positivity. In any case, the date of relapse is the date of 1<sup>st</sup> positive assay.

☐ **cytogenetic relapse**

Presence of one or more t(9;22) positive metaphases with standard cytogenetics or hypermetaphase FISH and/or >5% cells with the BCR/ABL fusion gene by interphase FISH, in a patient lacking any evidence of the disease at haematological/clinical level (ie. haematological CR).

☐ **clinical relapse**

Clinical/Haematological relapse = Cytological and/or histological evidence of chronic phase disease in the marrow, blood, spleen and liver without infiltration of other organs. Cytogenetic and/or molecular confirmation of the presence of the disease is recommended unless any change in current therapy was performed because of the relapse. No additional chromosomal aberrations.

**Pre-emptive**

Pre-emptive treatment is a treatment in cases where a high risk of relapse is suspected, but still in remission at the time of treatment. The risk may be known from the biology of the disease in general or from specific changes indicative of the possibility of an impending relapse.

**Mixed chimaerism**

There is good evidence that persistent mixed chimaerism carries a high risk of relapse in acute leukaemia, although the presence of mixed chimaerism does not necessarily indicate an impending relapse. In particular in ALL, late after transplantation mixed chimaerism is compatible with the continuous remission of the leukaemia. However an increase of host type cells early after transplantation is highly indicative of an impending relapse in leukaemia patients. Mixed chimaerism in patients with a poor marrow function may herald rejection of the graft.

**ANTI-TUMORAL TREATMENT PRIOR TO DLI**

The effect of DLI is influenced by the prior treatment with anti-leukemic, anti-tumoral treatment, immunosuppressive treatment in the case of GvHD and treatment with cytokines like interferon- $\alpha$  and/or GM-CSF.

In the case of acute leukaemia or the acute phase of chronic leukaemia, chemotherapy may be necessary to gain time for immunotherapy with DLI. In AML/MDS the preferred treatment is low dose cytosine arabinoside which may induce partial remissions in about 50% of patients. The remaining patients require more intensive chemotherapy protocols including high dose cytosine arabinoside and anthracyclins. Alternatively the treatment with CD33 antibody (Mylotarg) may be considered.

In ALL mild chemotherapy like vincristine / prednisolone have not been successful and more aggressive chemotherapy may be required.

In CML the best choice for chemotherapy prior to DLI is the use of STI 571, a selective tyrosine kinase inhibitor which inhibits the malignant cells only. The best schedule seems the start with 200 mg daily escalating until response and DLI after two negative PCR tests 4 weeks apart.

**STATUS:**

The success of DLI depends very much on the condition of the patient, i.e. the history, presence or absence of GvHD, the state of chimaerism and the general condition.

**GvHD present**

In case the leukemic relapse occurs in the presence of GvHD – chronic or acute – the risk of aggravating GvHD by DLI is high and the chance of controlling leukaemia by DLI is low. Therefore the actual extent of GvHD has to be scored. The presence of significant liver or lung disease is a contraindication for DLI. Less severe GvHD can be treated by immunosuppression prior to DLI.

**Full chimaerism present**

Chimaerism (all BM cells are from donor origin) is a prerequisite for the success of DLI. Chimaerism should be studied by usual methods, i.e. cytogenetics, FISH for heterochromosomes, short tandem repeats (STR) for sex identical donors. Most importantly the chimaerism of T-cells should be documented. Blood groups and other markers are not reliable to answer this question.

**On-going immunosuppressive therapy**

Immunosuppressive treatment may be required to treat GvHD present prior to DLI. This treatment may consist of cyclosporine A and prednisolone, antithymocyte globulin or CD3 antibody. Immunosuppressive treatment of the patient may reinforce the effect of DLI by eliminating tolerant T-cells in the host.

**SCHEDULE**

Donor T-cells may be given as a single transfusion or as multiple transfusions. If in multiple transfusions, the dose of donor T-cells may be fixed or may start from very low doses ( $10^5 - 10^6$ ) and escalate every time. The dose of T-cells is based on the measurement of CD3-positive cells, the dose of stem cells on that of CD34-positive cells.

INFUSION 1 (OR SINGLE INFUSION) - - INFUSION 2 - - INFUSION 3

**Cytokines in the period immediately following this infusion**

Conventional treatment of CML consists of subcutaneous application of interferon- $\alpha$ . Interferon- $\alpha$  controls CML in a yet unknown mechanism, it up-regulates the expression of co-stimulatory molecules and activates macrophages. This way it may stimulate the activity of transfused T-cells.

GM-CSF (granulocyte-monocyte colony stimulating factor) stimulates the expression of co-stimulatory molecules on the myeloid blasts and induces differentiation of myeloid blast cells to antigen-presenting cells. This way the activity of transfused lymphocytes is directed to the leukemic cell.

T-cells may be specifically sensitized against relevant antigens of the host hematopoietic cells or the leukaemia cell. The procedures are laborious and the activity of these cells may be reduced after sensitization and expansion.

Less laborious is the activation of T-cells and NK cells by the treatment with interleukin-2 in vitro or the combination of interferon- $\gamma$  and interleukin-2 (CIK cells).

Please check any of the cytokines given immediately after each infusion.

## POST DLI COMPLICATIONS

**MYELOSUPPRESSION**

*(Defined as any of the following: WBC  $<1 \times 10^9/L$ ; Platelets  $<20 \times 10^9/L$ ; Reticulocytes  $<0.2\%$ )*

Complications of DLI may be myelosuppression characterised by a drop in leukocyte counts, platelet counts, reticulocyte counts and a hypocellular marrow. It is more frequent in haematological relapse than in cytogenetic relapse and it may result from a graft-versus-leukaemia reaction or a graft-versus-host reaction against host hematopoietic cells. Myelosuppression in the course of GvHD usually does not respond to the transfusion of marrow or blood stem cells.

If myelosuppression was present at any time but resolved and is not present on the date of assessment, please make sure you answer "Yes" to Myelosuppression.

**AGvHD/cGvHD MANIFESTATION**

Graft versus Host Disease (GvHD) occurs in up to 60% of patients treated with DLI, it is severe enough (GvHD grade =II) to require immunosuppressive treatment in about 40%. DLI produces GvHD more frequently after transplantation of T-cell depleted stem cells. GvHD occurs also more frequently, if DLI are given after cytoreductive or immunosuppressive conditioning. GvHD after DLI differs in its clinical appearance from GvHD after conditioning and stem cell transplantation. It is rarely acute and tends to be more chronic.

For aGvHD grading refer to the Allograft section of this manual.

For cGvHD extent refer to the Follow up section of this manual.

## STATUS AFTER DLI

Outcome of treatment with DLI will be recorded on day 100, at 6 months, 12 months and yearly thereafter. The outcome variables are survival, control of the disease, chimaerism and the occurrence of complications like myelosuppression, GvHD, infections, lung disease and other disease and immune restitution.

CR = complete remission

PR = partial remission

NR = no response/stable disease

For disease status specific to different diagnosis, please see the corresponding section in this manual.

### **SURVIVAL STATUS**

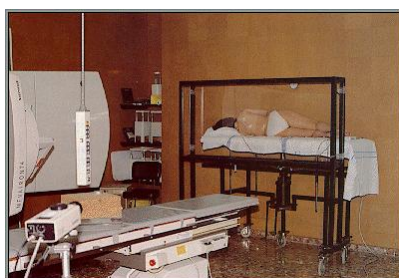
If patient has died, please make sure the follow up form corresponding to his/her diagnosis has been filled in.

## ALL DISEASES

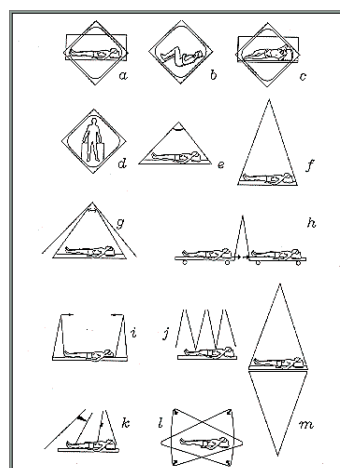
## TOTAL BODY IRRADIATION

Total Body Irradiation (TBI), also known as Whole-Body Radiation, involves the use of external radiation sources that produce penetrating rays of energy to deliver a relatively uniform amount of radiation to the whole body without damaging the overlying skin and surrounding tissue at risk. It is delivered before or after chemotherapy and prior to the stem cell transplantation (SCT). For cancers that are widely disseminated throughout the body, such as leukaemia, lymphoma etc, TBI is of great importance as a conditioning regimen, destroying the tumour cells and suppressing the function of the host cells in preparation for the SCT.

TBI is a very complex technique. Due to the large irradiation fields needed to treat the whole patient, this technique requires a different approach in comparison to any other standard radiotherapy treatment.



- The final technique is imposed by the facilities of the institution.



- Different irradiation positions can be used depending on the source and bunker characteristics.

It requires the contribution of many scientific disciplines (Haematology, Radiotherapy, Medical Physics) and for this reason the TBI form is divided into two main parts:

- The first one is filled in by the haematologist, (first 5 lines)

	EBMT Centre Identification Code (CIC) of haematology unit : ..... CENTRE	
	Hospital .....	Unit ..... CENTR
UPN	Hospital Patient Number .....	UIC (if known) ... ID IDAA
FAMNAME	Initials .....	Date of birth ..... DATPATBD
	yyyy mm dd	
DATBMT	Date of transplant ..... - ..... - ..... Date chemo started: ..... - ..... - ..... DCHMCON	
	yyyy mm dd	yyyy mm dd

It contains parameters on patient specific data (CIC, Family name, Date of birth, etc.) as well as the date of the transplant and the date the TBI related **chemotherapy** started (usually a few days before the date of transplant).

- The second part is filled in by the Medical Physicists. This means that the necessary information to fill in the rest of the form must be obtained from the Radiotherapy/Medical Physics Department.

To start this section, some more general data are required, including the CIC of the radiotherapy unit which may differ from that of the haematology unit if TBI could not be delivered at the same hospital (very common in paediatric cases).

	EBMT Centre Identification Code (CIC) of radiophysicist unit (if CIC exists) : ..... VCIRADI	
VNAMEHOS	Hospital .....	Unit ..... VRDPHNA
VPHONE	Telephone .....	Fax .....

From this section onwards, the form is divided into:

- Target Volume (Whole body, including the skin)
- Normal Tissue (Lung, organ most at risk)
- Normal Tissue (Other organs at risk)

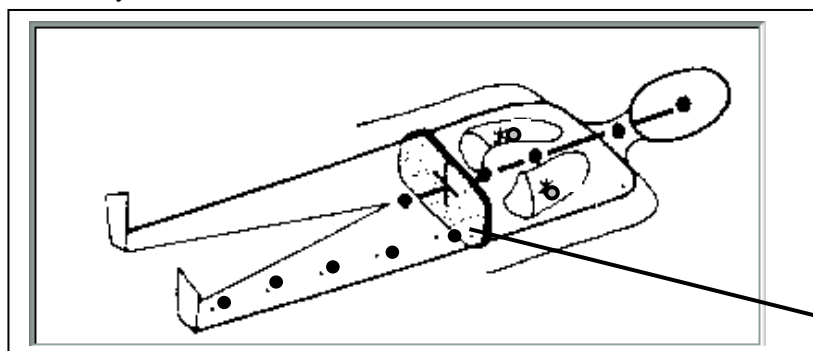
## I TARGET VOLUME WHOLE BODY (including the skin)

Every treatment of radiotherapy needs planning (*Radiotherapy Treatment Planning, RTP*). This involves the choosing and arranging of radiation beams around the patient, usually with the help of CT or MRI images, in order to provide a high dose (energy deposition per mass) at the site of the tumour and as low a dose as possible to everywhere else. As part of the RTP, the *Target Volume* is defined and it contains the tumour. In our case, the “tumour” are the malignant cells, the normal immunocompetent cells and the normal stem cells spread out all around the body, therefore, the target volume is the whole body, including the skin.

VTBIDOSE

T.B.I. DOSE ... .. Gy

For conventional treatments, the *Tumour Dose* can refer to the dose at the tumour, and in our case, the TBI Dose is specified as the dose at the midpoint of the abdomen at the level of the umbilicus (the specification point). It is a very important parameter for the success of the treatment and results are usually between 5 Gy and 15 Gy.



● Reference point representative of 50% of the lung volume.

✱ TBI Dose specification point at the midpoint of the abdomen at the level of the umbilicus

● Dose reference points for determination of longitudinal dose variation along the body midline.

Plane specification to define the transverse dose homogeneity.

In addition, a homogeneous distribution of dose within the target volume (the whole body) is required. Maximum and minimum dose values along the body midline and in the transverse section containing the specification point (shown in the diagram above) should be determined. These deviations are to be completed on the form in terms of percentages (+ for maximum and – for minimum) with respect to the TBI Dose specification point (100%). For example, if we obtain a maximum reading of 107% at a foot reference point, and a minimum at the mediastinum of 94%, then in the spaces left below for *Longitudinal (along the body midline)* the data would be: + 7 % and - 6 %, and the same for the transverse homogeneity.

### HOMOGENEITY

TRANSVERSE (across transverse plane through the specification point)

+... ..% - ... ..%

LONGITUDINAL (along the body mid-line)

+... ..% - ... ..%

VHGRPC,  
VHGLNPC

In many cases, to accomplish the TBI treatment additional irradiation beams are needed (known as *Boosts*) to over-irradiate certain regions of high risk, such as the spleen or the rib cage due to its high concentration of malignant cells.

In this section, the form is designed to record if as part of the RTP, the mentioned organs were intended to receive a dose varying from the TBI dose by 10% or more.

IF VARYING FROM T.B.I. DOSE BY 10% OR MORE:

ORGAN

DOSES

1. SPLEEN

... .. %

2. RIB CAGE

... .. %

3. ....

... .. %

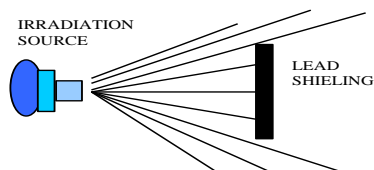
ESTIMATED RELATIVE VOLUME ... .. %

VOTHORPCD

## II NORMAL TISSUE

## LUNG, ORGAN MOST AT RISK

The TBI Dose in combination with chemotherapy may exceed the tolerance of certain organs such as the lungs, the eyes, etc. In particular, the lungs are the most critical organ at risk and *interstitial pneumonitis* (an inflammation of the connective tissue of the lung caused by radiation exposure) is one of the main causes of death after SCT using TBI. Furthermore, the low density of the lungs results in the delivery of a dose which is higher than the dose prescribed to the target volume. Thus there is a very steep dose-effect relationship with lung toxicity, (20% increase in toxicity with only a 5% higher dose).

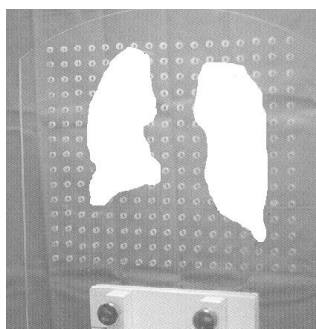


For this reason *shielding* (the use of blocks of lead to prevent the radiation going through, see diagram) is often used and this ensures that a critical volume of lung is not irradiated.

In this section of the form, the mean total lung dose needs to be indicated as well as an estimate of the physical shielded volume (shielding might not be used in all sessions). The lung dose is specified at a point which is representative for more than 50% of its volume.

**RADLUNB**  
**VLNGSHVL**

Lung Dose (mean of total at reference points of both lungs): ..... Gy  
Shielded Volume (estimated) : .....%



- Organs at risk, such as the lungs, need to be maintained below certain limits. This is achieved by the use of shielding with lead as shown.



The radiation treatment can be given in one single dose or in different divided doses; this is *fractionated radiation*. In this section of the form the number of fractions need to be recorded as well as the number of days that these sessions cover (if it is done in one fraction, then it would be *one*), the starting date and the minimum time interval between the sessions (in hours).

TBI can cause acute health effects during the first six weeks following a single exposure. The type and severity of the effects depend, among other things, on the dose, the *Dose Rate* (the next parameter that needs to be filled in the form) and the individual's sensitivity to radiation. The Dose Rate can be defined as the dose delivered divided by the time taken to deliver it. It is of less importance in fractionated than in continuous TBI.

From the beginning of radiobiology, the effect of dose rate has been known to be important. The best quotient of dose/time during the treatment is unknown. Dose Rate should be measured in two ways and it should be clear which dose rate is being specified: whether the average of the mean value of every session, which is interrupted by the patient positioning or any other cause (i.e. *mean dose rate*), or the dose rate from the machine and reaching the lung reference point (i.e. *instantaneous dose rate*). The dose rate regimens can be classified in terms of:  $\leq 0.06$  Gy/min (LOW);  $\geq 0.06$  Gy/min (HIGH). The mean dose rate (i.e. 0.042 Gy/min) will always be smaller than the instantaneous one (0.258 Gy/min) since there will always be a patient positioning interruption, even for single fraction treatments.

### III NORMAL TISSUE OTHER ORGANS AT RISK

VEYEDOSE  
VKIDNEYD  
VCNSDOSE  
VORGDOSE

ORGAN	DOSES (with respect to 100%, if varying from T.B.I. by 10% or more)
1. EYES LENSES	... .. %
2. KIDNEYS	... .. %
3. C.N.S.	... .. %
4. ....	... .. %

Finally, this section needs to be filled in if the dose to the stated organs is different by more than 10% of the specified TBI dose. This is of great importance to study the influence of these doses on the appearance of the "Late Effects" associated with these organs, such as, for example, cataracts. An empty slot is left at the bottom (4. ....) for you to enter any organ not listed which you consider to be of relevance.

### IV COMMENTS (e.g. irregular parameters, if parameters vary or not constant)

.....

.....

To conclude, any additional comments can be added here. For example, this would be the space provided to mention that: "After TBI, extra irradiation by boost was given to the retro orbital region" (this is done when eye shielding during TBI is used to prevent cataracts and the retro-orbital zone of high risk is left sub-irradiated).

### REFERENCES

- *Total Body Irradiation prior to Bone Marrow Transplantation*. F. Sánchez Doblado et al. EBMT
- <http://huespedes.cica.es/huespedes/ebmt-tbi/report-index.html>
-

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**APPENDIX I****KARNOFSKY SCALE**[{Return to Performance score}](#) [{Return to Survival status}](#)

<b>Score</b>	<b>Performance Status</b>
100	Normal, no complaints or evidence of disease
90	Able to perform normal activity; minor signs and symptoms of disease
80	Able to perform normal activity with effort; some signs and symptoms of disease
70	Cares for self, unable to perform normal activity or to do active work
60	Requires occasional assistance but is able to care for most of own needs
50	Requires considerable assistance and frequent medical care
40	Requires special care and assistance; disabled
30	Hospitalization indicated, although death not imminent; severely disabled
20	Hospitalization necessary; active supportive treatment required, very sick
10	Fatal processes progressing rapidly; moribund
0	Dead

**LANSKY SCALE**

<b>Score</b>	<b>Performance Status</b>
100	Fully active, normal
90	Minor restrictions in physically strenuous activity
80	Active, but tires more quickly
70	Both greater restriction of and less time spent in play activity
60	Up and around, but minimal active play; keeps busy with quieter activities
50	Gets dressed but lies around much of the day, no active play but able to participate in all quiet play and activities
40	Mostly in bed; participates in quiet activities
30	In bed; needs assistance even for quiet play
20	Often sleeping; play entirely limited to very passive activities
10	No play; does not get out of bed
0	Unresponsive

## APPENDIX II

Data	International Unit Système Internationale	Indicative range	Other unit	Conversion	
				Other to IU Multiply by	IU to Other Multiply by
				Values have to be multiplied by:	
white blood cells✓	10 <sup>9</sup> /L	4– 11.2	1/mm <sup>3</sup> 10 <sup>3</sup> /cc	0.001	1000
neutrophils	10 <sup>9</sup> /L	0.7 – 7.6	1/mm <sup>3</sup> 10 <sup>3</sup> /cc	0.001	1000
Platelets ✓	10 <sup>9</sup> /L	130 – 400	10 <sup>3</sup> /mm <sup>3</sup> 10 <sup>3</sup> /μL	1	1
hemoglobin	mmol/L	7.5 – 11	g/dL	0.6206	1.611
			g/L	0.06206	16.11
creatinine✓	μmol/L	58- 161	mg/L	8.84	0.113
			mg/100 mL mg/dL	88.4	0.0113
creatin. clearance✓	mL/s	1.24 – 2.08	mL/min	0.0167	60
			cc/min	1	1
total bilirubin✓	μmol/L	1.9- 18.	mg/L	1.71	0.585
			mg/ 100 mL mg/dL	17. 1	0.0585
sodium✓	mmol/L	132 – 151	mEq/L	1	1
			g/L	43.5	0.023
			mg./100 mL	0.435	2.3
potassium✓	mmol/L	3.1- 5.2	mEq/l	1	1
			g/L	25.6	0.039
			mg/ 100 mL	0.256	3.91
calcium✓	mmol/L	2.3-2.8	mEq/L	0.5	2
			g/L	25.	0.04
			mg/ 100 mL mg/dL	0.25	4.01
Urea (BUN)✓	mmol/L	3.0 – 6.5	mg/dL	0.357	2.8
Uric acid✓	μmol/L	120 -420	mg/L	5.948	0.168
			mg/100 mL mg/dL	59.48	0.0168
Glucose ✓	mmol/L	3.4-5.6	mg/L	0.0055	180
			mg /100 mL mg/dL	0.055	18.0
total proteins✓	g/L	65-80	g/dL	10	0.1
albumin✓	g/L	32- 52	g/dL	10	0.1

**APPENDIX III****Standard intensity conditioning regimens (established regimens)**[{Return to myeloablative}](#)

<b>Leukemias:</b>	Busulfan 16 mg/kg + cyclophosphamide 120-200 mg/kg Cyclophosphamide 120 mg/kg fractionated, TBI 12 Gy (fractionated) ± ATG Etoposide VP-16 30-60 mg/kg, TBI 12 Gy (fractionated) or 10 Gy in single dose
<b>CLL</b>	TBI 10-14 Gy; Busulfan 16 mg/kg; ± other agent
<b>Lymphomas:</b>	BEAM polychemotherapy ± ATG <ul style="list-style-type: none"> <li>- BCNU (300 mg/m<sup>2</sup>)</li> <li>- Etoposide (6-800 mg/m<sup>2</sup>)</li> <li>- Ara-C (800-1600 mg/m<sup>2</sup>)</li> <li>- Melphalan (100-140 mg/m<sup>2</sup>)</li> </ul> CBV polychemotherapy ± ATG <ul style="list-style-type: none"> <li>- Cyclophosphamide</li> <li>- Etoposide</li> <li>- BCNU</li> </ul> Busulfan 16 mg/kg + cyclophosphamide 120-200 mg/kg ± ATG Cyclophosphamide 120 mg/kg + TBI 12 Gy (fractionated) ± ATG
<b>Myeloma:</b>	200 mg/m <sup>2</sup> Melphalan
<b>Solid tumours:</b>	Cyclophosphamide 60-120 mg/kg Fludarabine 120 mg/kg
<b>Aplastic anemia</b> (non-constitutional)	Cyclophosphamide 200 mg/kg ± ATG
<b>Congenital disorders:</b>	Busulfan 14-16 mg/kg + cyclophosphamide 120-200 mg/kg ± ATG
<b>Autoimmune diseases:</b>	
MS:	BEAM ± ATG <ul style="list-style-type: none"> <li>- BCNU (300 mg/m<sup>2</sup>)</li> <li>- Etoposide (6-800 mg/m<sup>2</sup>)</li> <li>- Ara-C (800-1600 mg/m<sup>2</sup>)</li> <li>- Melphalan (100-140 mg/m<sup>2</sup>)</li> </ul>
Others:	Cyclophosphamide 200 mg/kg + ATG Busulfan 16 mg/kg + cyclophosphamide 120-200 mg/kg + ATG Cyclophosphamide 120 mg/kg + fractionated TBI 12 Gy + ATG

**Non myeloablative (reduced intensity) conditioning regimens**

Only regimens with dosages equal or below these limits should be classified as non myeloablative HSCT.

<b>Leukemias</b>	Busulfan $\leq 8$ mg/kg $\pm$ TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
	Cyclophosphamide $\leq 60$ mg/kg $\pm$ TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
	TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
<b>Lymphoma</b>	Busulfan $\leq 8$ mg/kg $\pm$ TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
	Cyclophosphamide $\leq 60$ mg/kg $\pm$ TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
	TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
	Melphalan 140 mg/m <sup>2</sup> + fludarabine
	Melphalan 70-140 mg/m <sup>2</sup> +/- purine analogue +/- Campath 1H
	TBI 2 Gy + FLU 90 mg/m <sup>2</sup> iv
<b>Myeloma</b>	Melphalan $\leq 100$ mg/m <sup>2</sup> $\pm$ purine analogue $\pm$ ATG
<b>Aplastic anemia non-constitutional:</b>	Cyclophosphamide 1200 mg/m <sup>2</sup> $\pm$ ATG
<b>Solid tumours</b>	Busulfan $\leq 8$ mg/kg $\pm$ TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
	Cyclophosphamide $\leq 60$ mg/kg $\pm$ TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG
	TBI $\leq 6$ Gy (fractionated) $\pm$ purine analogue $\pm$ ATG

There are no general recommendations for other disease categories.

**Example of a sequential conditioning regimen:**

The following sequence is a borderline case, but considered by the Definitions Committee to be Standard (myeloablative) conditioning

	D-15	D-14	D-13	D-12	D-11	D-10	D-9	D-8	D-7	D-6	D-5	D-4	D-3	D-2	D-1	D0
<b>Cytarabine</b>	2 x 1000 mg/m <sup>2</sup>	2 x 1000 mg/m <sup>2</sup>	2 x 1000 mg/m <sup>2</sup>	2 x 1000 mg/m <sup>2</sup>												
<b>Fludarabine</b>	30 mg/m <sup>2</sup>	30 mg/m <sup>2</sup>	30 mg/m <sup>2</sup>	30 mg/m <sup>2</sup>												
<b>Amsacrine</b>	100 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	100 mg/m <sup>2</sup>												
<b>Thymoglobuline</b>												0,5 mg/kg	2,5 mg/kg	3 mg/kg		
<b>Busulfan</b>								4 x 0,8 mg/kg	4 x 0,8 mg/kg	4 x 0,8 mg/kg	4 x 0,8 mg/kg					

## **APPENDIX IV**

### **CYTOGENETICS INFO**

Key nomenclature: <http://www.slh.wisc.edu/clinical/cytogenetics/basics/>

Further explanation: <http://chromodisorder.org/intro-to-chromosomes>