EBMT Registry

Immunosuppressive treatment (IST) annual follow-up

Guide to the completion v2.4 of the EBMT data collection form: IST_FU_annual_Core_Extended_v2.3

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EBMT Registry

EBMT Clinical Research & Registry Department

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Table of Contents

Introduction

Please make sure you have already checked the **Introduction to the EBMT Registry Completion Guidelines** document latest version available under *Manuals and Reference Documents* section on EBMT website.

Immunosuppressive treatment (IST) Annual/Unscheduled Follow-Up

The IST annual/unscheduled follow-up form must be submitted to the EBMT Registry database annually after an IST episode or at time of patient death, whichever occurs first. If an additional line of IST is given the a new IST D0 form should be filled in. IST follow-up forms should then be completed for the latest IST given.

If there are fluctuations in the disease status during the follow-up period and the centres deem it relevant, or if the patient is discharged from the centre and/or moves to another centre, an additional report may be provided between the standard reporting schedule.

Date of follow-up

Report the follow-up date which is the closest to the annual follow-up assessment post-IST. If the patient died, enter the date of death. If the patient was lost to follow-up, enter the date the patient was last seen.

Survival status

Indicate if the patient is last known to be **Alive** or **Dead**. If the patient is lost to follow-up, tick the box for Lost to follow-up.

Date of the last IST for this patient

Please provide the start date of the immunosuppressive treatment episode for which this follow-up is being reported.

Main cause of death

Check only one main cause that applies. In case of doubt, consult a physician. If none of the answers in the table match, tick the box **Other cause of death** and specify it. If the cause of death is not known, select **Unknown**.

The following main causes of death can be reported (check only one):

- Relapse or progression/persistent disease;
- **Secondary malignancy**
- **IST-related** – death caused by complications or infections after an immunosuppressive episode (also indicate the treatment related cause);
- **HCT-related** - death caused by complications or infections after transplant (also indicate the treatment related cause).

Select treatment related cause

In case of IST- or HCT-related cause of death, specify if the cause of death was related to (select all that apply):

- Graft versus Host Disease;

If the main cause of death was IST-related, graft versus host disease can not be selected.

- **Non-infectious complication;**
- Infectious complication;
- Other treatment related cause of death; Please specify.

Infectious complication

If the cause of death was related to an infectious complication, select all types of infection that apply:

- **Bacterial infection;**
- **Viral infection;**
- **Fungal infection;**
- **Parasitic infection;**
- **Infection with unknown pathogen.**

Extended dataset

Was an autopsy performed?

Check **No**, if no autopsy has been performed. Check **Yes** if an autopsy was performed. Check the box **Unknown** if it is not known whether or not an autopsy was performed.

Best response

Best response after this IST

Report the best response achieved since the immunosuppressive treatment, but before any subsequent treatment, even if the patient got worse again afterwards. This includes the response observed before or without any subsequent treatment. The definitions of the best responses for severe and moderate aplastic anaemia can be found in table 1. For congenital bone marrow failures, no formal response criteria are available. If the best response to this IST was already reported on a previous annual IST FU form then it is not necessary to report it again.

Response	**Definition**	
	Severe aplastic anaemia	**Moderate aplastic anaemia**
Stable disease (no change/no response/loss of response)	Not meeting any of the response criteria defined below	Not meeting criteria of partial or complete response
Complete Remission (CR)	All of the following: ● No evidence of clonal evolution, by marrow cytogenetic and flow cytometry ● Peripheral blood counts: haemoglobin >10 gr/dL, absolute neutrophils >1.0 x 10^9/L, platelets >100 x 10^9/L	All of the following: ● Haemoglobin normal for age ● Neutrophils >= 1.5 x 10^9/L ● Platelets >= 150 x 10^9/L
Partial Remission (PR):	All of the following: ● No longer meeting criteria for diagnosis of SAA ● Transfusion independence (defined as no need of any PRBC or platelet transfusion) ● Peripheral blood counts: haemoglobin >8 gr/dL, absolute neutrophils >0.5 x 109/L, platelets >20 x 109/L	At least one of the following: ● Transfusion independence (if previously required) doubling or normalisation of at least one cell line ● Increase above baseline by: 3 g/dl haemoglobin and 0.5 x 109/L neutrophils and 20 x 109/L platelets

Haematological improvement (HI); NIH partial response:	No longer meeting criteria for diagnosis of SAA	No longer meeting criteria for diagnosis of MAA
Relapse / Progression:	Any of the following events after a haematological response (CR or PR): ● Meeting again the criteria for SAA ● Requirement of transfusion support (if not due to independent medical conditions) ● Decrease in any of the peripheral blood counts as follows: Decrease to less than 50% of the medium sustained count during remission if: absolute neutrophils <1.0 x 10^9/L, platelets <50 x 10^9/L; or Or in any case if: absolute neutrophils <0.5 x 10^9/L , platelets <20 x 10^9/L The peripheral blood count decrease must be: ● Not due to any independent concomitant medical condition ● Demonstrated in at least 3 tests over a period of 2 weeks ● Not responding to re-introduction of low dose cyclosporin A	After a haematological response (CR or PR), once again meeting the criteria for MAA

Table 1. Definitions of best responses.

Date best response first observed

Report the date the best response was first observed. The response date is the date that the sample or image was taken for assessing the response. If the patient is in CR, enter the date CR was achieved or assessed. If the date is unknown, select the **Unknown** checkbox.

Is the date that the PR was achieved/first observed known?

If a CR was achieved within the d100 period after the IST then please indicate if the date that the PR was achieved is known. If there was a PR observed in the patients blood values prior to achieving the CR and the date is known then please select **Yes**. If it is not known which date the patient reached PR prior to the CR then please select **No**. Please note that, although all patients will reach PR prior to achieving CR, this question asks specifically whether or not this PR was observed/measured in the patients blood values. **Note:** This question can be skipped if the date that the PR was achieved/first observed has already been reported on the IST d100 form.

Date PR achieved/first observed

If the answer to the previous question is **Yes**, indicate the date that the prior PR was achieved/first observed.

Transfusions

Red blood cells (RBC) transfusions given since last follow-up

Indicate if any RBC transfusions were given since the last follow-up by selecting **No** or **Yes**. Answer **Unknown** if it is not known whether or not RBC transfusions were given since the last follow-up.

RBC

Count and indicate the total number of red blood cells (RBC) units transfused since the last follow-up by selecting the appropriate checkbox:

- **< 20 units;**
- **20 - 50 units;**
- **> 50 units.**

Answer **Unknown** if there is no information on RBC transfusions in the patient's medical records.

RBC irradiated

Indicate if the RBC were irradiated (answer **Yes**), not irradiated (answer **No**) or if it is unknown (answer **Unknown**).

Platelet transfusions given since last follow-up

Indicate if any platelets transfusions were given since last follow-up by selecting **No** or **Yes**. Answer **Unknown** if it is not known whether or not platelets transfusions were given since the last follow-up.

Number of platelets transfusions given

Count and indicate the total number of platelets transfused since the last follow-up by selecting the appropriate checkbox:

- **< 20 units;**
- **20 - 50 units;**
- **> 50 units.**

Answer **Unknown** if there is no information on platelet transfusions in the patient's medical records.

Platelets irradiated

Indicate if platelets were irradiated (answer **Yes**), not irradiated (answer **No**) or if it is unknown (answer **Unknown**).

Extended dataset

Haematological tests

Date tests performed

Report the date when the haematological tests were performed.

Haemoglobin (g/dL)

Report the haemoglobin level in g/dL. Check the box **Not evaluated** if the haemoglobin level was not assessed. If this result is unavailable, check the box **Unknown**.

Was haemoglobin transfused within 4 weeks before assessment?

Indicate if any RBC transfusions were given within 4 weeks before the annual assessment by selecting **No** or **Yes**. Answer **Unknown** if it is not known whether or not RBC transfusions were given during this follow-up.

Platelets (10^9 cells/L)

Indicate the number of platelets x 10^9/L or make a corresponding mark if it was **Not evaluated**. If this result is unavailable, check the box **Unknown**.

Were platelets transfused within 7 days before assessment?

Indicate if any platelets transfusions were given within 7 days before the annual assessment by selecting **No** or **Yes**. Answer **Unknown** if it is not known whether or not platelets transfusions were given during this follow-up.

Neutrophils (10^9 cells/L)

Indicate the number of neutrophils x 10^9/L or make a corresponding mark if it was **Not evaluated**. If this result is unavailable, check the box **Unknown**.

Reticulocytes (10^9 cells/L)

Indicate the number of reticulocytes x 10^9/L or make a corresponding mark if it was **Not evaluated**. If this result is unavailable, check the box **Unknown**.

Ferritin (ng/ml)

Report the ferritin level in ng/mL. Check the box **Not evaluated** if the ferritin level was not assessed. If this result is unavailable, check the box **Unknown**.

First relapse after IST

Report the first relapse or progression after the last episode of IST; since multiple IST episodes may be given in an individual patient, relapses after each episode must be reported. If the first relapse/progression was reported at previous follow-up, leave this section without answer and proceed to the last disease status section.

First relapse/progression of Aplastic Anaemia (detected by any method)

First relapse means the first relapse that occurs after the first CR or PR has been achieved. If the patient has never had a CR or a PR, the status of the disease cannot be relapsed, but it can be progression and thus it is also covered in this section. If a first relapse or progression occurred, select **Yes**. If this did not occur, select **No**. If the first relapse to this IST has already been reported on a previous follow-up form, then it does not need to be reported again.

Date of first relapse/progression

Report the date of the first relapse/progression since the IST. If this information is unavailable, select **Unknown**.

Disease status at this Follow-Up

Disease status this follow-up

Select the disease status that reflects the status at the time of this assessment that is being reported. If disease status was not assessed at this follow-up enter **Not evaluated.** The disease status can be reported according to the same criteria outlined in the Best response section of this guideline.

Complications since last Follow-Up

Adverse events/non-infectious complications grade 3-5 observed (based on CTCAE grades)

Check the latest version of Common Terminology Criteria for Adverse Events (CTCAE) available at NCI webpage. Answer **Yes** if there were any adverse events and non-infectious complications grade 3-5 or mild-very severe observed since the last report.

Answer **No (grade 0-2)** if there were no adverse events/non-infectious complications grade 3-5 or mild-very severe observed.

Observed

If **Yes** was answered to the previous question, indicate per each adverse event/non-infectious complication in the table below if it was observed (answer **Yes**) or not (answer **No**). If there was any adverse event/non-infectious complication observed that is not mentioned in the table, check the box **Other** and specify the event in the text field in English. Answer **Unknown** if it is not known whether or not the specified complication occurred.

Observed, yes

If **Yes** was answered to the previous question, indicate whether the adverse event/non-infectious complication developed during this assessment (select **Newly developed**) or if the adverse event/non-infectious complication was **ongoing since the previous assessment**.

Maximum CTCAE grade

For each adverse event that was observed, select the maximum CTCAE grade that was observed in this follow-up period. For veno-occlusive disease (VOD) please indicate if it was mild, moderate, severe, very severe or fatal. Please select **Unknown** if the grade/severity of the complication is not known.

Onset date

Report the onset date of the event when the adverse event was first observed during this follow-up period (only newly developed events). Select **Unknown** if the date is unavailable.

This also applies if the complication was resolved early in this follow-up period.

Extended dataset

Resolved

Please indicate whether or not the complication has been resolved. Answer **No** if the complication has not yet been resolved. Answer **Yes,** if the complication has been resolved. Answer **Unknown** if it is not known whether or not the complication was resolved.

Stop date

If **Yes**, please also provide the date that the complication was resolved. Select **Unknown** if the stop date is unavailable.

Secondary malignancies and Autoimmune disorders

Did a secondary malignancy or autoimmune disorder occur?

Answer **No** if neither secondary malignancy nor autoimmune disorder has been observed after this IST episode and if unknown, answer Unknown. Answer **Yes** if secondary malignancy or autoimmune disorder occurred and specify:

Was it a secondary malignancy or autoimmune disorder?

Indicate whether it is a secondary malignancy or autoimmune disorder.

Date of diagnosis

Indicate the date of diagnosis. In case the date is not known, report **Unknown**.

Was this disease an indication for a subsequent HCT/CT/IST?

If the answer is **No**, complete the respective non-indication diagnosis form. If the answer is **Yes**, complete the relevant indication diagnosis form.

Bone marrow investigations

In this section, specify the results of the bone marrow examinations.

Bone Marrow Investigation

If any bone marrow investigation was performed, answer **Yes** and provide details in subsequent questions of this section. If not, select **No** and proceed to the next section.

Date of bone marrow investigation

Report the date the bone marrow investigation was done.

Type of bone marrow investigation:

Specify the type of bone marrow investigation performed, whether it was:

- Cytology; - Identification and counting of cells in the bone marrow sample
- Histology;
- Both cytology and histology.

Type of dysplasia

Dysplasia is the presence of cells that are abnormal in size, shape, organisation, and/or number. Indicate for each of the following bone marrow cell lines if dysplasia was present **Yes** or absent **No**:

- Erythroid - red blood cells and their precursors
- Granulocyte - granular white blood cells (leukocytes): neutrophils, eosinophils, and basophils
- Megakaryocyte - precursor to platelets that reside in the bone marrow

If the dysplasia for that cell line has not been evaluated in the bone marrow, select **Not evaluated,** and if unknown, answer **Unknown**.

Bone marrow assessments

Cellularity in the bone marrow aspirate

Report the result of the cellularity assessment performed by aspiration test by indicating if the bone marrow was **Acellular**, **Hypocellular**, **Normocellular**, **Hypercellular** or it had **Focal cellularity**.

Usually, the examination of the BM aspirate is done by a haematologist. The results can be found in the haematology lab report.

Cellularity	Description
Acellular	Absence of bone marrow cells (“dry tap”)
Hypocellular	Bone marrow has fewer cells than normal or expected
Normocellular	Bone marrow has normal cellularity
Hypercellular	Bone marrow has more cells than normal or expected
Focal cellularity	Bone marrow has fewer cells than normal or expected but with the local normal cellularity

Table 2. Definitions of bone marrow cellularity.

If the cellularity in the bone marrow aspirate was not evaluated, report **Not evaluated**. Select **Unknown** in case it is not known if the cellularity was assessed or not.

Cellularity in the bone marrow trephine

Report the result of the cellularity assessment performed by trephine biopsy by indicating if the bone marrow was **Acellular**, **Hypocellular**, **Normocellular**, **Hypercellular** or it had **Focal cellularity** (see the table above).

The results of the bone marrow trephine biopsy can be found in the pathology report.

If the cellularity in the bone marrow trephine was not evaluated, report **Not evaluated**. Select **Unknown** in case it is not known if the cellularity was assessed or not.

Fibrosis on bone marrow biopsy

Indicate if the bone marrow biopsy revealed any signs of fibrosis. Select **No**, if the biopsy did not show features of fibrosis. If the biopsy revealed histological features of fibrosis select **Mild**, **Moderate** or **Severe** depending on the fibrosis severity grade.

The results of the bone marrow biopsy can be found in the pathology report.

Select **Not evaluable** if the sample could not be analysed. If fibrosis was not evaluated, report **Not evaluated**. Select **Unknown** in case it is not known if the fibrosis was assessed or not.

CD34+ cell count percentage (%)

Indicate the percentage of CD34+ cells in the bone marrow sample. If the cell count was not assessed, report **Not evaluated**. Select **Unknown** in case it is not known if the cell count was measured or not.

Blast count percentage (%)

Indicate the percentage of blast cells in the bone marrow sample. If the cell count was not assessed, report **Not evaluated**. Select **Unknown** in case it is not known if the cell count was measured or not. If the precise blast count is not available, please indicate if the percentage blasts in the bone marrow sample was below or above 5%.

Chromosome analysis

Chromosome analysis done at follow-up

In this section describe the results of the most recent complete chromosome analysis (performed during this follow-up period).

No - the chromosome analysis has not been done;

Yes - the chromosome analysis has been performed prior to treatment;

Unknown - it is unknown whether the chromosome analysis has been done or not.

Output of analysis

Select **Separate abnormalities** for focused analysis or **Full karyotype** for comprehensive assessment.

What were the results?

Normal - the results of the analysis were normal.

Abnormal - at least one of the results has been found to be abnormal. In addition, indicate the number of abnormalities present in the most recent analysis with abnormal results* (**number of abnormalities present**).

Failed - If the chromosome analysis was performed but failed *If more than one analysis has been done since the last follow-up, indicate **abnormal results** 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.

Date of chromosome analysis

Indicate the date of the chromosome analysis mentioned above. If the chromosome analysis was not done/failed or it is unknown if it was performed, leave the field blank. If the date of chromosome analysis is unavailable, select **Unknown**.

Chromosome analysis details

See the cytogenetics form or ask the cytogenetics team and consult your physician.

If chromosome analysis was performed, indicate for each abnormality in the table whether it was **Absent** or **Present**. If a chromosome abnormality was not evaluated, report **Not evaluated**. Mark **Unknown** if the information is unavailable.

If a chromosome abnormality was checked, but not listed as an option in the table, select **Other** and specify the abnormality in the text field, marking whether it was **Absent** or **Present**.

Transcribe the complete karyotype

If it is necessary, transcribe the complete karyotype according to the International System for Human Cytogenetic Nomenclature (ISCN).

Molecular marker analysis

Molecular marker analysis done at follow-up

If molecular markers were assessed at this follow-up, select **Yes** and provide details in subsequent questions of this section. If they were not assessed, select **No**. Select **Unknown** if it is unknown whether the analysis of the molecular markers has been done or not.

Date of molecular marker analysis

If applicable, report the date of the molecular marker analysis. If the date is unavailable, select **Unknown**.

Molecular marker analysis details

If molecular marker analysis was performed, indicate for each marker in the table whether it was **Absent** or **Present**. If a molecular marker was not evaluated, report **Not evaluated**.

If a molecular marker was evaluated, but not listed as an option in the table, select **Other** and specify the marker, indicating whether it was **Absent** or **Present**.

TP53 mutation type

If **TP53** mutation is present, indicate the mutation type if known. A TP53 mutation is considered a multi hit if it fulfils one of the following criteria:

- 2 or more distinct mutations of TP53 with a VAF of ≥ 10%
- 1 mutation and 1 deletion involving the TP53 locus

- 1 mutation with VAF ≥ 50%
- 1 mutation with complex karyotype

A TP53 mutation is considered single hit if either one of the following criteria is fulfilled:

- a single TP53 mutation with VAF < 50%
- loss of 17p13 involving TP53 locus without TP53 mutations If the lab report does not specify the

type, select **Unknown**.

PNH Tests since last Follow-Up

PNH test done

Report if PNH test was done in the follow up period or not. If it is not known if the PNH test was performed please select **Unknown.**

Date of PNH test

If the answer to the previous question is **Yes**, indicate the date of the PNH test. In case the date is not known, report **Unknown**.

PNH diagnostics by flow cytometry

Blood cells that have been affected by PNH are known as PNH clone cells. Indicate if the clone was absent or present by selecting the respective check box. If it is not known whether or not the PNH clone is absent or present, report **Unknown.**

Size of PNH clone in percentage (%)

If the **Clone present** option is selected, specify also the **Size of the clone** in percentage (%) (PNH clone size refers to the proportion of PNH-affected cells versus normal cells within the total cell population). This information can be found in the haematology report.

Flow cytometry assessment done on

Indicate the type of cells used for the PNH test by selecting one of the options from the list: Red blood cells (RBC) or Granulocytes. If both RBC and granulocytes were tested please select **Both.** If flow cytometry was done on other cells, select **Other** and specify the cell type in English.

Clinical manifestation of PNH

If there are any clinical manifestations of PNH, select **Yes**, if not, select **No**.

Clinical manifestations of PNH 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 the bowel, oesophagus, or other muscles, as well as erectile dysfunction.

Date of clinical manifestation of PNH

If the answer to the previous question is Yes, report the date when the clinical manifestation was first reported. In case the date is not known, report **Unknown**.

Anti-complement treatment given?

Indicate if any anti-complement treatment was given to the patient by selecting either **No** or **Yes**. Including compounds that inhibit the complement system, for example: C-5 inhibitors (Eculizumab & Ravulizumab) and C-3 inhibitors (Pegcetacoplan). If the anti-complement treatment that has been given is not listed please select: **Other; specify**.

If anti-complement treatment was given, please provide details.

Drug

Select the drug name from the list of options or use **Other** field and report the generic drug/agent name(s) in the textbox in English.

Please consult the List of Chemotherapy Drugs, Agents and Regimens on the EBMT website for drug/agent names. This document provides alternative names for many of the drugs/agents. Once you have found the drug/agent of interest on the list, add its database name to the table.

New or ongoing

Select **New drug administration** if the anti-complement treatment was started during this follow-up period. If the treatment has been reported in a previous follow-up form and was not stopped at that follow-up, select **Ongoing since previous assessment.**

Start date

Report the date when the treatment was started during this follow-up period. Select **Unknown** if the start date is not known.

This also applies if the treatment was stopped early in this follow-up period.

Treatment stopped

Indicate if anti-complement treatment stopped. In case this information is unavailable, report **Unknown**.

Stop date

If the answer to the previous question is **Yes**, indicate the date when anti-complement treatment stopped. In case the date is not known, report **Unknown.**

If there were more drugs given during one line of treatment use copies of the page for the paper form. It is also possible to add additional fields in the online EBMT Registry application to report multiple drugs here.