

# HCT day 100 follow-up

**Guide to the completion of the EBMT  
data collection form: HCT\_FU\_D100\_v1.0**

22 August 2023

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EBMT Registry

EBMT Clinical Research & Registry Department



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## HCT Day 100 follow-up

The HCT Day 100 form may be filled in paper version and must be submitted online into the EBMT Registry database 100 days post-transplant or at time of patient death, whichever occurs first.

### 1. Date of follow-up:

Report the follow-up date which is the closest to the Day 100 follow-up assessment post-HCT. 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 alive.

### 2. 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**.

## Best Response

### 3. Best clinical/biological response after HCT

Report the recipient's best response achieved after HCT, even if the patient got worse again afterwards. This includes the response observed before or without any subsequent treatment. If the best response after the HCT has not been evaluated, select **Not evaluated**. If the best response after the HCT is unknown, select **Unknown**.

The best response is often achieved in the first 100 days. However, for some diseases the best response to HCT may take longer and shall be reported in the first annual follow-up form (e.g. multiple myeloma). For all indication diagnoses except for inherited disorders, data managers should report the best response achieved as per the date of follow-up. In case HCT was performed for inherited disorders, this section can be left blank.

If the patient has relapse/progression post-HCT and receives therapy for the disease relapse/progression, the response to that additional therapy should not be reported in this section. The best response prior to the relapse /progression should be reported here. The response should be captured before the start of unplanned treatment of underlying disease.

#### 3.1. 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 assessed. If the date is unknown, select the **Unknown** checkbox.

## Recovery

### 4. Absolute neutrophil count (ANC) recovery (neutrophils $\geq 0.5 \times 10^9$ cells/L)

Absolute neutrophil count (ANC) recovery is considered to take place when the number of neutrophils in the patient's peripheral blood rises to at least  $0.5 \times 10^9$  cells/L. Please note this is regardless of the use of growth factors and neutrophils level should be confirmed by three consecutive laboratory values obtained on different days.

Answer **No** (and proceed to question 4.1.) if:

- An autologous reconstitution has taken place – particularly in a RIC (Reduced Intensity Conditioning) setting – where the donor cell origin needs to be confirmed (in an allograft setting only).
- The stem cell source is either PB or BM and the ANC  $< 0.5 \times 10^9$  cells/L by Day +28. (both in an allograft and in an autograft setting).
- The stem cell source is CB and the ANC  $< 0.5 \times 10^9$  cells/L by Day +42 (both in an allograft and in an autograft setting).

Answer **Yes** if the absolute count of neutrophils post-HCT is higher or equal to  $0.5 \times 10^9$  cells/L for 3 laboratory values (and proceed to question 4.2.).

If the absolute count of the patient's neutrophils was never below  $0.5 \times 10^9$  cells/L, the answer **Never below** must be chosen instead of answer **Yes**. This may happen in non-myeloablative transplants.

Mark the ANC as **Unknown** if it was not assessed post-HCT.

#### 4.1. Date of the last assessment:

Indicate the date of the last assessment of the patient's neutrophils level.

#### 4.2. Date of ANC recovery:

The date to be entered is the first date out of the 3 consecutive neutrophil counts above  $0.5 \times 10^9$  cells/L were recorded on different days. This date must be at least 7 days after the last transfusion containing neutrophils.

### 5. Platelet reconstitution (platelets $\geq 20 \times 10^9$ cells/L):

Indicate whether or not there was platelet reconstitution achieved that is confirmed by 3 consecutive blood tests where absolute count of platelets is  $\geq 20 \times 10^9$  cells/L. All dates should reflect no transfusions in the previous 7 days.

Answer **No** (and proceed to question 5.1.) if the platelet count was  $< 20 \times 10^9$  cells/L or if platelet transfusions were administered in the previous 7 days.



Answer **Yes** (and proceed to question 5.2.) if the platelet count  $\geq 20 \times 10^9$  cells/L was achieved and sustained for 3 consecutive laboratory values, obtained on different days without platelet transfusions administered in the previous 7 days.

Answer **Never below**, if the recipient's platelets never dropped below  $20 \times 10^9$  cells/L at any time post-HCT and a platelet transfusion was never required. If the recipient's platelet count drops below  $20 \times 10^9$  cells/L and/or the recipient received a platelet transfusion even once, do not use this option. This option is only applicable in the 100 day follow-up reporting period.

Answer **Unknown** if recipient's platelets were not assessed post-HCT.

### 5.1. Date of the last assessment:

Indicate the date of the last assessment of the patient's platelets level.

### 5.2. Date of platelet reconstitution:

The date to be entered is the first date out of the 3 consecutive platelets counts  $\geq 20 \times 10^9$  cells/L checked on different days and after 7 days without platelet transfusion. Mark as **Date unknown** if it is confirmed by medical record that patient achieved platelet reconstitution but the exact date of the first test with platelets counts  $\geq 20 \times 10^9$  cells/L is not known.

### 5.3. Date of the last platelet transfusion:

Indicate the date when the patient received the latest platelet infusion within the 100 day follow-up period.

## Complications since the Last Report

### GvHD

This section (questions 6 - 6.3.7) shall be completed only if the patient received an allogeneic HCT.

### 6. Did graft versus host disease (GvHD) occur? (for allogeneic HCT only)

Select **Yes** if GvHD occurred and proceed to question 6.1. If it did not occur select **No** and proceed to question 7 (non-infectious complications).

Graft-versus-host disease (GvHD) refers to a clinical syndrome caused by the response of transplanted donor allogeneic cells to histocompatibility antigens expressed on tissues of the transplantation recipient. Acute GvHD refers to the appearance of an allogeneic inflammatory response in exclusively three organs: the skin (inflammatory maculopapular erythematous skin rash), the liver (hyperbilirubinemia due to cholestatic jaundice), and the gastro-intestinal (GI) tract (upper and/or lower GI tract manifestations). The diagnosis must occur in the absence of manifestations of cGvHD and should ideally be supported by positive histological findings.

cGvHD is based on either the presence of specific diagnostic signs or distinctive signs accompanied by additional confirmation (e.g. biopsy or other objective diagnostic test) in at least one target organ (skin & appendages, mouth, eyes, genitalia, esophagus, lungs and muscles & fascia). Detailed definitions are described in the 2014 NIH Consensus (1) and 2018 EBMT—NIH—CIBMTR Task Force statement on standardized terminology (2).

## 6.1. Did the patient receive a systemic immunosuppressive treatment for GvHD?

Indicate if the patient received a systemic immunosuppressive treatment for GvHD. If the answer is Yes, specify also:

### *6.1.1. Date treatment started:*

Report here the date the systemic immunosuppressive treatment for GvHD started.

### *6.1.2. Immunosuppression ongoing:*

Indicate whether systemic immunosuppressive treatment for GvHD is still ongoing as per the date of this follow-up report. Mark as **Unknown** if this is not known.

## 6.2. Acute GvHD:

Indicate if aGvHD occurred.

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 usually develops within the first 100 days, it can also appear later on.

### *6.2.1. Date of onset:*

If aGvHD occurred, report here the date of onset.

### *6.2.2. Maximum observed organ severity score:*

Select for each organ listed in the table the observed severity score. If another site was also affected, answer **Yes** in **Other site affected** and specify this site in the text field in English.

The maximum grade for acute graft versus host disease (aGvHD) is defined according to the stages presented by the skin, liver, lower and upper GI tracts and can be found in table 1.

Organ	Stage	Description
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	Generalized erythroderma (> 50% BSA) plus bullous formation and desquamation >5% of BSA
Liver	0	Total serum bilirubin < 34 µmole/L (< 2 mg/dL)
	1	Total serum bilirubin 34–50 µmole/L (2 to 3 mg/dL)
	2	Total serum bilirubin 51–102µmole/L (3.1 to 6 mg/dL)
	3	Total serum bilirubin 103–255 µmole/L (6.1 to 15 mg/dL)
	4	Total serum bilirubin >255 µmole/L (> 15 mg/dL)
Lower gut	0	Diarrhea < 500 mL/day or <3 episodes/day for adults or diarrhea <10 mL/kg/day or <4 episodes/day for children
	1	Diarrhea 500–999 mL/day or 3–4 episodes/day for adults or diarrhea 10–19.9 mL/kg/day or 4–6 episodes/day for children
	2	Diarrhea 1000–1500mL/day or 5–7 episodes/day for adults diarrhea 20–30 mL/kg/day or 7–10 episodes/day for children
	3	Diarrhea >1500 mL/day or >7 episodes/day for adults or diarrhea > 30 mL/kg/day or >10 episodes/day for children
	4	Severe abdominal pain with or without ileus or grossly bloody stools (regardless of stool volume)
Upper gut	0	No or intermittent anorexia or nausea or vomiting
	1	Persistent anorexia or nausea or vomiting

Table 1, aGvHD grading system per organ (2)

*6.2.3. Overall maximum grade observed:*

Select the overall maximum grade that was observed. If it is not known which overall maximum grade was observed, select **Unknown**.

The overall grade (or the stage of skin, liver and gut) should be mentioned in the patients' file. If not clearly stated, ask the treating physician. You should report the maximum grade seen during the relevant period being studied as calculated from table 2.

Grade							
1	Skin stage 1 or 2	AND	Liver stage 0	AND	Upper gut stage 0	AND	Lower gut stage 0
2	Skin stage 3	AND/OR	Liver stage 1	AND/OR	Upper Gut stage 1	AND/OR	Lower gut stage 1
3	Any skin	AND	Liver stage 2 or 3	AND/OR			Lower gut stage 2 or 3
4	Skin stage 4	OR	Liver stage 4	OR			Lower gut stage 4

Table 2, overall maximum grade for aGvHD (2)

*6.2.4. Steroid-refractory acute GvHD:*

Indicate if the patient experienced steroid-refractory acute GvHD or not. Steroid refractory aGvHD is defined in the EBMT handbook (3) as: "Failure to respond to standard steroid doses (defined as progression within 3–5 days of starting treatment or an incomplete response by 7–14 days) or recurrence after initial dose reduction (steroid dependence)".

*6.2.5. Date of aGvHD resolution:*

If the acute GvHD resolved, please report the date on which it was thought to have resolved completely. If it is still ongoing, select **Ongoing**.

**6.3. Chronic GvHD:**

Indicate if chronic GvHD occurred or not.

Answer **No** if the patient has never had an episode of cGvHD.

If the answer is **Yes**, specify also:

*6.3.1. Date of onset:*

If cGvHD occurred, report here the date of onset.

*6.3.2. Maximum NIH score during this period:*

Indicate if the maximum NIH score during this period was **Mild**, **Moderate** or **Severe**. If the score is unknown, select **Unknown**.

The NIH scoring system was first published in 2005 and was updated in 2014 and 2022. As described in the 2014 Diagnosis and Staging Working Group report (1), eight classical organs or

sites (skin, mouth, eyes, lungs, musculoskeletal system, gastrointestinal tract, genitourinary tract, and liver) 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. Indicate the maximum NIH score during this period, as per the results of these measurements. Instructions for physicians on assessing the NIH score can be found in the EBMT handbook (1,4) or table 3.

Mild cGvHD	1 or 2 organs involved with no more than score 1 AND Lung score 0
Moderate cGvHD	3 or more organs involved with no more than score 1 OR At least 1 organ (not lung) with a score of 2 OR Lung score 1
Severe cGvHD	At least 1 organ with a score of 3 OR Lung score of 2 or 3

Table 3, assessing the maximum NIH score (1)

In 2022 the NIH consensus (5) recognized atypical manifestations of chronic GvHD, which should be placed in the section ‘other’ below the list of organs involved. Atypical manifestations do not contribute to the global severity score.

*6.3.3. Date maximum NIH score:*

Report the date the maximum NIH score was observed.

*6.3.4. Maximum observed organ severity score:*

Select for each organ in the table the observed severity score. If another site was affected, answer **Yes** in **Other site affected** and specify this site in the text field.

Use the NIH scoring system as described in 6.3.2.

*6.3.5. Steroid-refractory chronic GvHD:*

Indicate if the patient experienced steroid-refractory chronic GvHD. Steroid refractory cGvHD is defined as “progression of cGvHD while on prednisone at  $\geq 1$  mg/kg/day for 1 to 2 weeks or stable GvHD on  $\geq 0.5$  mg/kg/day (or 1 mg/kg every other day) of prednisone for 1 to 2 months” (2).

*6.3.6. Date of cGvHD resolution:*

Report the date of cGvHD resolution. If it is not resolved yet, select **Ongoing**.

6.3.7. Was overlap syndrome observed (features of both chronic and acute GvHD):

If overlap syndrome was observed, select **Yes**. If overlap syndrome was not observed, select **No**.

Non-infectious complications

## 7. Did non-infectious complications occur during the follow-up period?

If no other non-infectious complication than GVHD did occur during the follow-up period, select **No** and proceed to question 8. If non-infectious complications with a CTCAE grade of at least 3 did occur or VOD or transplant-associated microangiopathy of any grade occurred, select **Yes** and report in the table below.

For adverse events not listed in the table, specify them in the **Other** text field.

### 7.1. Adverse event observed:

Specify for each adverse event listed whether it was observed or not. The CTCAE gradings (v5) can be found on the website of the NIH (6).

### 7.2. Maximum CTCAE grade observed:

Select for each adverse event the maximum CTCAE grade that was observed. If the grade is unknown, select **unknown**.

Note, for the following complications there are different grading systems to be used:

- Transplant-associated microangiopathy (7)
- Veno-occlusive disease (VOD)/ Sinusoidal obstruction syndrome (SOS) is diagnosed based on clinical criteria. The most recently proposed EBMT criteria include can be found in table 4.

Adults	Children			
<p>Classical SOS/VOD In the first 21 days after HSCT:  Bilirubin <math>\geq 2</math> mg/dL and two of the following criteria must be present:  Painful hepatomegaly  Weight gain <math>&gt;5\%</math>  Ascites</p> <p>Late onset SOS/VOD <math>&gt;21</math> Days after HSCT:  Classical VOD/SOS beyond day 21  Or  Histologically proven SOS/VOD  OR  Two or more of the following criteria must be present:  Bilirubin <math>\geq 2</math> mg/dL (or <math>34 \mu\text{mol/L}</math>)  Painful hepatomegaly  Weight gain <math>&gt;5\%</math>  Ascites  AND  Hemodynamical or/and ultrasound evidence of SOS/VOD</p>	<p>No limitation for time of onset of SOS/VOD  The presence of two or more of the following:  • Unexplained consumptive and transfusion-refractory thrombocytopenia  • Otherwise unexplained weight gain on three consecutive days despite the use of diuretics or a weight gain <math>&gt;5\%</math> above baseline value  • Hepatomegaly (best if confirmed by imaging) above baseline value  • Ascites (best if confirmed by imaging) above baseline value  • Rising bilirubin from a baseline value on 3 consecutive days or bilirubin <math>\geq 2</math> mg/dL within 72 h</p>			
Severity definition				
	Mild	Moderate	Severe	Very severe
Time since first clinical symptoms of SOS/VOD	$>7$ Days	5–7 Days	$\leq 4$ Days	Any time
Bilirubin ( $\mu\text{mole/L}$ )	$\geq 34$ and $<51$	$\geq 51$ and $<85$	$\geq 85$ and $<136$	$\geq 136$
Bilirubin kinetics			Doubling within 48 h	
Transaminases	$\geq 2 \times$ normal	$> 2$ and $\leq 5 \times$ normal	$>5$ and $\leq 8 \times$ normal	$>8 \times$ Normal
Weight increase	$< 5\%$	$\geq 5\%$ and $<10\%$	$\geq 5\%$ and $<10\%$	$\geq 10\%$
Renal function	$<1.2 \times$ baseline at transplant	$\geq 1.2$ and $<1.5 \times$ baseline at transplant	$\geq 1.5$ and $<2 \times$ baseline at transplant	$\geq 2 \times$ baseline at transplant or others signs of MOD/MOF

Table 4, diagnostic criteria for SOS and VOD (8)

No grading needs to be marked for Pure red cell aplasia.

### 7.3. Onset date:

Report the onset date when the adverse event was observed.

## Infectious complications

### 8. Did infectious complications occur during the follow-up period?

Answer **yes**, if any infectious complications occurred during the follow-up period, which includes previously unreported infections and reactivation of previously resolved infections.

Answer **no**, if no infectious complications occurred during the follow-up period, or if the infectious complication occurred in the previous follow-up period and remained or was resolved in this follow-up period.

Please note that the following infections do NOT need to be reported:

- Minor ophthalmologic bacterial infections (e.g. conjunctivitis treated topically; blepharitis treated topically; stye treated topically)
- External otitis treated topically
- Otitis media treated with oral antibiotics
- Isolated lip herpes simplex
- Bacterial tonsillitis or pharyngitis treated orally
- Laryngitis without viral identification managed at home by inhalations or without any intervention
- Upper respiratory tract infection (URTI) without viral/bacterial identification managed at home
- Bilateral cervical lymph node enlargement concurrent with URTI that resolved without specific treatment, together with the resolution of URTI
- Local superficial wound infection resolved under topical antibiotics (including impetigo)
- Minor skin bacterial infections (e.g. folliculitis; acne)
- Minor fungal skin infection (e.g. candidal intertrigo treated topically)
- Diaper rash treated with local antifungals
- Candidal balanitis treated topically
- Vaginal candidiasis treated topically or with a single oral dose
- Asymptomatic bacteriuria due to a pathogen not multi-resistant
- Single low urinary tract infection treated orally without need for hospitalization
- Phlebitis following peripheral intravascular infusion that resolved after intravascular removal without treatment with antibiotics
- Any isolate that is considered part of the normal flora of the place (oral cavity, vagina, skin, stools) except if it carries an antimicrobial resistance that has clinical implications (induce isolation precautions or a pathogen-directed therapy)

### 9. Bacterial infection

Indicate if the patient had a bacterial infection in the follow-up period after the treatment (after lymphodepleting/conditioning regimen) took place. Report here only bacterial infections with microbiological documentation, otherwise they shall be reported as infection with unknown pathogen.



### 9.1. Start date

Report the date a first positive blood or other relevant culture or diagnostic sample was obtained. In case a diagnostic sample was obtained with a delay since the symptoms of infection started – report here the date when symptoms attributable to this infection started (e.g. patient with pneumonia, urine test for legionella was sent after a few days and the test result was positive).

In case an infection was found for the first time at autopsy, use the date of death, unless you can identify the date when the symptoms attributable to this infection were reported for the first time.

### 9.2. Type of bacteria

Select the type of bacteria by marking if it is gram-positive, gram-negative or other (see the list in Appendix 1 of the form or available in the database).

### 9.3. Pathogen

Select the bacterium that caused the infection from the list in Appendix 1 of the form or available in the database. Choose the most specific option. If the pathogen cannot be found, choose the 'Other' option and enter its name in a textbox. Always report the full name of the bacterium. Please note that some bacteria appear several times but with the emphasis on their resistance pattern.

### 9.4. Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark unknown if it is not possible to identify. Clinical implications are at least one of the following: symptomatic infection in the relevant organ/system, the need for pathogen-directed therapy, or the need for the isolation precautions for infections.

#### *9.4.1. Infection with clinical implications, yes:*

Select the clinical implication(s) of the infection from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;
- Isolation precautions.

### 9.5. Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 2 of the form or available in the database.

Please note that the impact of an infection can differ greatly depending on its localisation, and therefore, localisation is essential and must be reported!

The CTCAE version that was used for the current form is version 5.0. Additional information on the CTCAE scoring can be found on the NIH website (6).

### 9.6. Intravascular catheter-related infection

Indicate if the infection was related to a central venous catheter (CVC). Please note that bacteremia can be CVC-related or not CVC-related. The definition for the CVC-related bacteremia requires one of the following:

- The same organism growing from at least 1 percutaneous blood sample culture and from the catheter tip
- 2 blood samples for culture are obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CVC-related bacteremia criteria for quantitative blood cultures: a colony count of microbes grown from blood obtained through the catheter hub being at least 3-fold greater than the colony count from blood samples obtained from a peripheral vein
- 2 blood samples for culture are obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CVC-related bacteremia criteria for differential time to positivity (DTP): growth of microbes from blood obtained through the catheter hub being detected at least 2 hours before microbial growth is detected in blood samples obtained from a peripheral vein
- 2 quantitative blood cultures of samples are obtained through 2 catheter lumens, with the colony count for the blood sample drawn through one lumen being at least 3-fold greater than the colony count for the blood sample obtained from the second lumen (9).

#### *9.6.1. Specify*

If the infection was related to an intravascular catheter, select the type of CVC infection from the list in Appendix 3 or available in the database.

### 9.7. Infection resolved

Indicate if the infection was resolved during the follow-up period. By resolved it is understood that the patient is free of symptoms/signs of this infection or symptoms/signs of this infection are under control, and negative diagnostic tests were obtained in case the investigation was repeated, and the relevant imaging is compatible with expected improvement.

If there was more than one bacterial infectious episode during the follow-up period, repeat these questions for the subsequent infection.

## 10. Viral infection

Indicate if the patient had a viral infection in the follow-up period after the treatment (after lymphodepleting/conditioning regimen) took place. Report here only infections with

microbiological documentation, otherwise they shall be reported as infection with unknown pathogen.

### 10.1. Start date

Report the date a first positive viral test (usually PCR or antigen) was obtained. In case a diagnostic sample was obtained with a delay since the symptoms of infection started – report here the date when symptoms attributable to this infection started (e.g. patient with encephalitis, with a positive PCR in cerebrospinal fluid done 10 days after symptoms started).

In case an infection was found for the first time at autopsy, use the date of death, unless you can identify the date when the symptoms attributable to this infection were reported for the first time.

### 10.2. Pathogen

Select the virus that caused the infection from the list in Appendix 1 of the form or available in the database. Choose the most specific option. If the pathogen cannot be found, choose the 'Other' option and enter its name in a textbox. Always report the full name of the virus.

*10.2.1. If the pathogen was CMV/EBV: was this a primary infection in a previously seronegative patient?*

Answer yes, if the patient's serology tests (CMV IgG, EBNA, EBV IgG) and (if taken) PCR tests were negative before the treatment (start of lymphodepleting/conditioning regimen) took place.

### 10.3. Infection with clinical implications

Indicate if the infection had clinical implications (or not), or mark unknown if it is not possible to identify. Clinical implications are at least one of the following: symptomatic infection in the relevant organ/system, the need for pathogen-directed therapy, or the need for the isolation precautions for infections.

*10.3.1. Infection with clinical implications, yes:*

Select the clinical implication(s) of the infection from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;
- Isolation precautions.

### 10.4. Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 2 of the form or available in the database.

Please note that the impact of an infection can differ greatly depending on its localisation, and therefore, localisation is essential must be reported!

The CTCAE version that was used for the current form is version 5.0. Additional information on the CTCAE scoring can be found on the NIH website (6).

#### 10.5. Infection resolved?

Indicate if the infection was resolved during the follow-up period. By resolved it is understood that the patient is free of symptoms/signs of this infection or symptoms/signs of this infection are under control, and negative diagnostic tests were obtained in case the investigation was repeated, and the relevant imaging is compatible with expected improvement.

If there was more than one viral infectious episode during the follow-up period, repeat these questions for the subsequent infection.

### 11. Fungal infection

Indicate if the patient had a fungal infection in the follow-up period after the treatment (after lymphodepleting/conditioning regimen) took place. Report here only infections with microbiological documentation, otherwise they shall be reported as infection with unknown pathogen.

#### 11.1. Start date

Report the date a first positive culture, PCR test or galactomannan test was obtained, or the pathogen was first identified by its typical appearance in the tissue/specimen material. In case a diagnostic sample was obtained with a delay since the symptoms of infection started – report here the date when symptoms attributable to this infection started, or when this is not known, the date of the first imaging (e.g. CNS, lungs, or liver/spleen imaging for instance in hepatosplenic candidiasis in a patient with persistent fever and negative blood cultures).

In case an infection was found for the first time at autopsy, use the date of death, unless you can identify the date when the symptoms attributable to this infection were reported for the first time.

#### 11.2. Type of fungi

Select the type of fungal infection by marking if it is yeasts or moulds.

#### 11.3. Pathogen

Select the fungus that caused the infection from the list in Appendix 1 of the form or available in the database. Choose the most specific option. If the pathogen cannot be found, choose the 'Other' option and enter its name in a textbox. Always report the full name of the fungus. Please note that there is an option for mould infection diagnosed based on positive galactomannan only without additional microbiological confirmation.

#### 11.4. Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark unknown if it is not possible to identify. Clinical implications are at least one of the following: symptomatic infection in the relevant organ/system, the need for pathogen-directed therapy, or the need for the isolation precautions for infections.

##### *11.4.1. Infection with clinical implications, yes:*

Select the clinical implication(s) of the infection from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;
- Isolation precautions.

#### 11.5. Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 2 of the form or available in the database.

Please note that the impact of an infection can differ greatly depending on its localisation, and therefore, localisation is essential and must be reported!

The CTCAE version that was used for the current form is version 5.0. Additional information on the CTCAE scoring can be found on the NIH website (6).

#### 11.6. Intravascular catheter-related infection

Indicate if the infection was related to a central venous catheter (CVC). Please note that fungemia can be CVC-related or not CVC-related. The definition for the CVC-related fungemia requires one of the following:

- The same organism growing from at least 1 percutaneous blood sample culture and from the catheter tip
- 2 blood samples for culture are obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CVC-related fungemia criteria for quantitative blood cultures: a colony count of fungi grown from blood obtained through the catheter hub being at least 3-fold greater than the colony count from blood samples obtained from a peripheral vein
- 2 blood samples for culture are obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CVC-related fungemia criteria for differential time to positivity (DTP): growth of fungi from blood obtained through the catheter hub being detected at least 2 hours before fungal growth is detected in blood samples obtained from a peripheral vein

- 2 quantitative blood cultures of samples are obtained through 2 catheter lumens, with the colony count for the blood sample drawn through one lumen being at least 3-fold greater than the colony count for the blood sample obtained from the second lumen (9).

#### 11.6.1. Specify

If the infection was related to an intravascular catheter, select the type of CVC infection from the list in Appendix 3 or available in the database.

### 11.7. Infection resolved?

Indicate if the infection was resolved during the follow-up period. By resolved it is understood that the patient is free of symptoms/signs of this infection or symptoms/signs of this infection are under control, and negative diagnostic tests were obtained in case the investigation was repeated, and the relevant imaging is compatible with expected improvement.

If there was more than one fungal infectious episode during the follow-up period, repeat these questions for the subsequent infection.

## 12. Parasitic infection

Indicate if the patient had a parasitic infection in the follow-up period after the treatment (after lymphodepleting/conditioning regimen) took place. Report here only infections with microbiological documentation, otherwise they shall be reported as infection with unknown pathogen.

### 12.1. Start date

Report the date a first positive antigen or DNA test was obtained or the first positive microscopic examination was performed. In case a diagnostic sample was obtained with a delay since the symptoms of infection started – report here the date when symptoms attributable to this infection started, or when this is not known, the date of the first imaging (e.g. CNS imaging for instance in Toxoplasmosis).

In case an infection was found for the first time at autopsy, use the date of death, unless you can identify the date when the symptoms attributable to this infection were reported for the first time.

### 12.2. Type of parasite

Select the type of parasitic infection by marking if it is protozoa or helminths.

### 12.3. Pathogen

Select the parasite that caused the infection from the list in Appendix 1 of the form or available in the database. Choose the most specific option. If the pathogen cannot be found, choose the 'Other' option and enter its name in a textbox. Always report the full name of the parasite.

## 12.4. Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark unknown if it is not possible to identify. Clinical implications are at least one of the following: symptomatic infection in the relevant organ/system, the need for pathogen-directed therapy, or the need for the isolation precautions for infections.

### *12.4.1. Infection with clinical implications, yes:*

Select the clinical implication(s) of the infection from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;
- Isolation precautions.

## 12.5. Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 2 of the form or available in the database.

Please note that the impact of an infection can differ greatly depending on its localisation, and therefore, localisation is essential and must be reported!

The CTCAE version that was used for the current form is version 5.0. Additional information on the CTCAE scoring can be found on the NIH website (6).

## 12.6. Infection resolved?

Indicate if the infection was resolved during the follow-up period. By resolved it is understood that the patient is free of symptoms/signs of this infection or symptoms/signs of this infection are under control, and negative diagnostic tests were obtained in case the investigation was repeated, and the relevant imaging is compatible with expected improvement.

If there was more than one parasitic infectious episode during the follow-up period, repeat these questions for the subsequent infection.

## 13. Infection with unknown pathogen

Indicate if the patient had an infection with unknown pathogen in the follow-up period after the treatment (after lymphodepleting/conditioning regimen) took place.

Use this section to report clinical infections without microbiological documentation, like pneumonia, cellulitis, etc.

### 13.1. Start date

Report the date the first signs or complaints were recorded or the first positive radiology was obtained. In case an infection was found for the first time at autopsy, use the date of death,

unless you can identify the date when the symptoms attributable to this infection were reported for the first time.

### 13.2. Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark unknown if it is not possible to identify. Clinical implications are at least one of the following: symptomatic infection in the relevant organ/system, the need for pathogen-directed therapy, or the need for the isolation precautions for infections.

#### *13.2.1. Infection with clinical implications, yes:*

Select the clinical implication(s) of the infection from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;
- Isolation precautions.

### 13.3. Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 2 of the form or available in the database.

Please note that the impact of an infection can differ greatly depending on its localisation, and therefore, localisation is essential and must be reported!

The CTCAE version that was used for the current form is version 5.0. Additional information on the CTCAE scoring can be found on the NIH website (6).

### 13.4. Intravascular catheter-related infection

Indicate if the infection was related to a central venous catheter (CVC). For example, a purulent infection of the exit site or tunnel, without isolation of pathogen.

#### *13.4.1. Specify*

If the infection was related to an intravascular catheter, select the type of CVC infection from the list in Appendix 3 or available in the database.

### 13.5. Infection resolved

Indicate if the infection was resolved during the follow-up period. By resolved it is understood that the patient is free of symptoms/signs of this infection or symptoms/signs of this infection are under control, and the relevant imaging is compatible with expected improvement.

If there was more than one infectious episode with an unknown pathogen during the follow-up period, repeat these questions for the subsequent infection.



## SARS-CoV-2 related questions

### 14. Did the patient receive a vaccination against SARS-CoV-2 after HCT?

Report if the patient received at least one vaccination dose against SARS-CoV-2 after the treatment (after lymphodepleting/conditioning regimen) took place.

#### 14.1. Number of doses

If the patient received a vaccination against SARS-CoV-2 after the treatment (after lymphodepleting/conditioning regimen) took place, report the number of doses that were administered after the treatment.

#### 14.2. Date of the last dose

If the patient received a vaccination against SARS-CoV-2 after the treatment (after lymphodepleting/conditioning regimen) took place, report the date the last dose was administered.

### 15. Did the patient have a SARS-CoV-2 infection after HCT (positive PCR or antigen test)?

Answer **Yes** to this question if the patient had a SARS-CoV-2 infection which was confirmed by PCR or an antigen test after the treatment (after lymphodepleting/conditioning regimen) took place, either symptomatic or asymptomatic.

#### 15.1. Date

Report the date the patient tested positive for SARS-CoV-2 after the treatment (after lymphodepleting/conditioning regimen) took place.

If there was more than one episode (new confirmed infection at least  $\geq 90$  days after the clearance of the previous one or at any time if evidence of a different variant), report the subsequent dates the patient tested positive after the treatment (after lymphodepleting/conditioning regimen) took place.

## Secondary Malignancies and Autoimmune Disorders

### 16. Did a secondary malignancy or autoimmune disorder occur?

Answer **No** if neither secondary malignancy nor autoimmune disorder has been observed after this HCT. Answer **Yes** if secondary malignancy or autoimmune disorder occurred and specify:

#### 16.1. 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.

## Graft Function

### 17. Early graft loss/failure (*engraftment followed by loss of graft within the first 100 days or no engraftment at all*):

If there was an early graft loss, select **Yes** and proceed to question 17.1. If an early graft loss was not observed, select **No**. Select **Unknown** if it was not checked. In both those cases proceed to question 18.

#### 17.1. Type of graft loss:

Report the type of the early graft loss by selecting **Primary** if there was no engraftment at all, or **Secondary** if it was observed after initial engraftment.

#### 17.2. Date of graft loss:

Report the date of the early graft loss.

### 18. Severe poor graft function

If observed severe poor graft function was observed, select **Yes** and proceed to question 18.1. If a late graft loss was not observed, select **No**. Select **Unknown** if it was not checked. In both those cases proceed to question 19.

Severe poor graft function is when despite evidence of complete donor chimerism post-allo HCT, there is persistent cytopenias and it is defined as follows: dependence on blood and/or platelet transfusions and/or growth factor support in the absence of other explanations, such as disease relapse, drugs, or infection (10).

#### 18.1. Date:

Report the date severe poor graft function was observed.

### 19. Percentage of donor cells (chimerism) at last follow up:

Answer this question only if the patient received an allogeneic transplant. Report the percentage of donor cells. If it was not evaluated, select **Not evaluated** and move on to question 22.

If lineage-specific data is present, please provide only overall chimerism value. If only lineage-specific values are available, please leave the field blank.

### 20. Chimerism test date:

Report the chimerism test date.

## 21. Source of cells tested:

Indicate if **Peripheral blood**, **Bone marrow** or **Other** cells were tested.

## Additional treatment including cell therapy

### 22. Did the patient receive any additional disease treatment since the last follow-up?

If the patient received additional disease treatment since the last follow-up, select **Yes** and proceed to question 14.1. If the patient did not receive additional disease treatment, select **No**.

#### 22.1. Date started:

Report here the date the additional disease treatment started.

### 23. Did the patient receive additional cell infusions?

If the patient received additional cell infusions, excluding a new HCT and/or CAR-T treatment, select **Yes** and proceed to question 23.1. If the patient did not receive additional cell infusions, select **No**.

#### 23.1. Is this cell infusion an allogeneic boost?

If the cell infusion was an allogeneic boost, select **Yes**. Otherwise select **No**.

An allogeneic 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 (in the case of inborn errors) OR there is conditioning (chemo and/or TBI), then it is considered to be a genuine transplant.

#### 23.2. Is this cell infusion an autologous boost?

If the cell infusion was an autologous boost answer **Yes** and proceed to question 24.3. If it was not an autologous boost, select **No**.

Autologous boost is infusion of pre-collected and stored autologous stem cells without conditioning.

#### 23.3. Date boost took place:

If applicable, report here the date the boost took place.

Note: If this cell infusion is not a boost, attach the Cell Infusion (CI) sheet available in Appendix 4, completing as many sheets as episodes of cell infusion that took place during this follow-up period; then continue with questions below.

## 24. Did the patient receive subsequent HCT/CT?:

If the patient received subsequent HCT/CT, either at your or another centre, select **Yes** and make sure that this subsequent treatment is registered using the appropriate HCT/CT form before proceeding.

If the patient did not receive subsequent HCT/CT, select **No**.

## 25. Radiotherapy:

If the patient received radiotherapy, select **Yes**. If the patient did not receive radiotherapy, select **No**. Select **Unknown** to mark that there is no information if the patient received radiotherapy or not.

## 26. Drugs/chemotherapy:

If the patient did not receive any drugs or chemotherapy, select **No** and proceed to 'Relapse/progression or significant worsening', starting at question 27.

If the patient did receive any drugs or chemotherapy, select **Yes** and complete the table by listing all chemotherapy/drugs given during one line of treatment. Report as many lines of treatment as applicable answering questions 26.1- 26.5.

### 26.1. Drug/regimen used:

Indicate here which drugs/regimens were given per each line of treatment. Please consult the LIST OF CHEMOTHERAPY DRUGS/AGENTS AND REGIMENS on the EBMT website for drugs/regimens names.

### 26.2. Start date:

Report the start date of each line of treatment when the drug(s)/regimen(s) were given.

### 26.3. Reason:

Indicate if the drug(s) was/were given for **Prophylaxis/preventive** reasons, **Relapse**, **Maintenance** or **Consolidation** reasons. If the drug/regimen was given, because of another reason which is not listed, select **Other** and specify the reason in the textbox.

### 26.4. Response to this line of treatment:

Report the response to this line of treatment by selecting one of the options:

- **Continued complete remission (CCR)**
- **Complete remission (CR)**
- **Partial remission**
- **No response / Stable disease / No change**
- **Disease progression.**

If it was not evaluated, select **Not evaluated**. If it is unknown what the response was to this line of treatment, select **Unknown**.

26.5. Response assessment date:

Report the response assessment date.

## Relapse/Progression or Significant Worsening

27. Was there a relapse/progression or significant worsening of organ function related to the primary disease after HCT?

Indicate if there was a relapse/progression or significant worsening of organ function related to the primary disease after HCT detected by any method. If the answer is **Yes**, proceed to questions 27.1. - 27.3. If the answer is **No**, proceed to question 28. If it was a continuous progression, select **Continuous progression since HCT**.

27.1. Date of first relapse/progression:

Report the date of the first relapse/progression since the HCT.

27.2. Type of relapse:

This question only needs to be answered for malignancies (inborn errors, haemoglobinopathies and autoimmune disorders are not considered malignant disorders). In case of relapse, specify the type of relapse by indicating if it was **Medullary only**, **Extra-medullary only** or **Both medullary and extra-medullary**. If the type of relapse is unknown, select **Unknown**.

27.3. Involvement at time of relapse (If the relapse was extra-medullary or both medullary and extra-medullary):

Report for each area of involvement, which are **Skin**, **CNS** (central nervous system), **Testes/Ovary**, **Other**, if it was involved at time of relapse answer **Yes**, or answer **No** if it was not involved. If answering Yes for the **Other**, specify it in the text field.

## Disease Status

28. Disease status at the last assessment before this follow-up or date of death:

Report the most recent disease status at the last assessment before this follow-up or date of death (whichever occurs first) by choosing one of the answer options:

- **Continued complete remission (CCR)**
- **Complete remission (CR)**

- **Partial remission**
- **No response / Stable disease / No change**
- **Disease progression.**

If the disease was not evaluated, select **Not evaluated**. If the disease status at the last assessment is unknown, select **Unknown**.

## 29. Was the disease detected by any method?

Select **No** if disease was not detected by any method (patient in CR). In order to answer No to this question, you need to have all tests done and all of them shall be negative. Select **Yes** if disease was detected by at least one method and proceed to questions 29.1 and 29.2.

### 29.1. Date of last assessment:

Report here the date disease was last assessed.

### 29.2. Method:

Select if the method used was **Haematological** (including Flow cytometry, Serum Protein Electrophoresis and Immunofixation), **Radiological**, **Molecular** or if it was an **Other** method not listed above. In case another method was used, specify it in the textbox in English.

## 30. Immunosuppression post-transplant? (*Allogeneic HCT only*)

Select **No** if the patient was not immunosuppressed post-transplant. Select **Yes** if the patient was receiving immunosuppressive therapy post-transplant and answer question 30.1.

### 30.1. End date:

Report the end date of the immunosuppressive therapy post-transplant. If it is still ongoing, select **Ongoing**.

## 31. Did transfusions stop after HCT? (*Haemoglobinopathies and bone marrow failures only*)

Select **No** if transfusions continued after HCT. If the patient was never transfusion dependent, select **Patient was never transfusion dependent**. If transfusions stop after HCT select **Yes** and proceed to question 31.1.

### 31.1. Did the patient go back to regular transfusion dependency?

Only applicable if the answer to the previous question is Yes. Select **No** if patient did not go back to regular transfusion dependency. Select **Yes** if the patient did go back to regular transfusion dependency and report the **first transfusion date**.

## Disease Status (*Leukaemias only*)

Complete this section only for patients with indication diagnosis leukaemia (either acute or chronic).

### 32. Minimal residual disease (MRD):

Select **Positive** if MRD test result was positive (disease detected) and answer question 32.1.

Select **Negative** if the MRD test results were negative (no disease was detected) after the HCT.

If MRD status was not tested, answer **Not evaluated** and proceed to question 36.

#### 32.1. Specify if MRD status was:

- **Increasing** ( $>1 \log_{10}$  increase between any 2 positive samples measured in the same tissue (PB or BM));
- **Stable** ( $<1 \log_{10}$  between any 2 positive samples measured in the same tissue (PB or BM));
- **Decreasing** ( $>1 \log_{10}$  decrease between any 2 positive samples measured in the same tissue (PB or BM)).

Change in MRD should be confirmed within 4 weeks, in a second consecutive sample, preferably with a BM sample.

### 33. Date MRD status evaluated:

If the MRD status was evaluated, report the date of MRD test.

### 34. Sensitivity of MRD assay:

If MRD status was evaluated, report the sensitivity of MRD assay, if it is:

- $<10^{-5}$
- $<10^{-4}$
- $<10^{-3}$

If the sensitivity is not listed, select **Other** and specify the sensitivity of MRD assay in the text box.

### 35. Method used:

If MRD status was evaluated, indicate which method(s) was/were used (check all that apply):

- **PCR;**
- **Flow cytometry;**
- **NGS.**

If a different method was used that is not listed, select **Other** and specify the method in the text box.

## Cause of Death (if patient died)

### 36. 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** 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;**
- **Cellular therapy-related** - death caused by complications or infections after cellular therapy (answer question 36.1);
- **HCT-related** - death caused by complications or infections after transplant (answer question 36.1).

#### 36.1. Select treatment related cause:

In case of Cellular therapy- or HCT-related cause of death, specify if the cause of death was related to:

- **Graft versus host disease (GvHD);**
- **Non-infectious complication;**
- **Infectious complication.**

##### *36.1.1. Infectious complication:*

If the cause of death was related to an infectious complication, select the type(s) of infections that apply:

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

## Cell Infusion Sheet

The following completion guidelines refer to the completion of appendix 4 of the day 100 form, the cell infusion sheet.

Please report each cell infusion episode performed during the follow-up period in a separate cell infusion sheet, completing as many sheets as episodes of cell infusion that took place. 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 2nd episode starting on the 1st day infusions were given after the change in indication.

Do not use this cell infusion sheet for any boost. All boosts shall be registered inside the HCT follow-up form.

### 1. Chronological number of CI episode for this patient:

Report the chronological number of this cell infusion episode for this patient.

### 2. Date of the first infusion:

Report the date of the first infusion within this episode.

### 3. Number of infusions within 10 weeks:

Report the number of infusions within 10 weeks. Count only infusions that are part of the same regimen and given for the same indication.

### 4. Source of cells:

Indicate if the source of cells are **allogeneic** and/or **autologous**, check all that apply.

### 5. Type of cells:

Select the type of cells, check all that apply:

- **Lymphocytes (DLI);**
- **Mesenchymal;**
- **Fibroblasts;**
- **Dendritic cells;**
- **NK cells;**
- **Regulatory T-cells;**
- **Gamma/delta cells;**
- **Virus-specific T-cells.**

If the type of cells is **virus specific T-cells**, also specify the virus the T-cells were directed against.

If the type of cells is not listed, select **Other** and specify the type of cells in the text field.

### 6. Disease status at time of this cell infusion:

Report the disease status at the time of this cell infusion. The options are the same as in question 28 of the main questions. If the disease status has not been evaluated, select **Not evaluated**. Select **Unknown** if the disease status at the time of this cell infusion is not known.

## 7. Indication:

Select all the indications for this cell infusion episode that apply:

- **Planned/protocol;**
- **Prophylactic;**
- **Treatment of acute GvHD;**
- **Treatment of chronic GvHD;**
- **Treatment PTLD, EBV lymphoma;**
- **Treatment for primary disease;**
- **Mixed chimaerism;**
- **Loss/decreased chimaerism;**
- **Treatment of viral infection other than EBV;**
- **Poor graft function;**
- **Infection prophylaxis.**

If the indication is not listed, select **Other** and specify it in the text field.

## 8. Acute GvHD - maximum grade (*after this infusion episode but before any subsequent cell infusion/HCT/CT*):

Indicate the maximum grade (Grade scale 0 - 4) of acute GvHD. If the grade is unknown but aGvHD is present, select **Present but grade unknown**. The grades are as in question 6.2 of the main questions.

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