

Autologous Haematopoietic Gene Therapy follow-up

**Guide to the completion of the EBMT data
collection form:**

GT_FU_v1.1

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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](#).

Gene Therapy follow-up

The Gene Therapy (GT) follow-up form may be filled in paper version and must be submitted online into the EBMT Registry database at 100 days, 6 months, 12 months, 18 months and then annually post-GT or at time of patient death, whichever occurs first.

Some sections of this form are relevant and should be submitted on particular follow-ups only. If so, it is mentioned in the subtitle of the respective section on the form. Otherwise (if no instruction as to what follow-up period the section covers), the questions of the section should be completed for every follow-up: Day 100, 6 Months, 12 Months, 18 Months and Annual/Unscheduled follow-up.

Date of follow-up

Report the date of this follow-up. If the patient died before the specific time point, enter the date of death. If the patient was lost to follow-up, enter the last contact date the patient was alive.

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**. If the patient died, please complete the following questions on the main cause of death.

Main cause of death

If the patient died, report only one main cause of death, even if it was considered to be a combination of various causes. If the cause of death is not known, select **Unknown**. The following main causes of death can be selected:

- **Relapse or progression/persistent disease;**
- **Secondary malignancy;**
- **CT-related** - death caused by complications or infections after cellular therapy;
- **HCT-related** - death caused by complications or infections after HCT;
- **GT-related** - death caused by complications or infections after Gene therapy;
- **IST-related** - death caused by complications or infections after immunosuppressive treatment as main treatment.

If none of the suggested options fit, select **Other** and specify the cause of death in the textbox in English.

Select treatment related cause

- **Graft versus Host Disease (GvHD);**
- **Non-infectious complication;**
- **Infectious complication.**

Infectious complication

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

Was an autopsy performed?

Select **Yes** if an autopsy was performed and select **No** if no autopsy was performed. If it is not known whether an autopsy was performed, select **Unknown**.

Assessment period covered by this report

Indicate which assessment period covers this report based on the time period in relation to the GT date.

You can select between the following:

- **Day 100:** 100 days post-GT. The data on this assessment should reflect the patient's status on the day the patient was last seen, closest to 100 days post-GT. If the patient died within 100 days, the data from the last date the patient was seen alive can be used.
- **6 months:** 6 months post-GT. The data on this assessment should reflect the patient's status on the day the patient was last seen, closest to 6 months post-GT. If the patient died within 6 months, the data from the last date the patient was seen alive can be used.
- **18 months:** 18 months post-GT;
- **24 months:** 24 months post-GT;
- **Annual or unscheduled follow-up** post-GT.
 - Annual follow-up: In principle each GT patient should receive a yearly follow-up after the GT. When reporting the annual follow-up in the Registry the follow-up that falls closest to the anniversary (yearly interval) of the GT should be reported.
 - Unscheduled follow-up: This form can also be used to report a follow-up that occurred outside of the scheduled follow-ups for a GT patient. For example, due to a death of a patient or patient proceeding to a subsequent HCT/GT. If a patient proceeds to a subsequent HCT/GT then a follow-up should be reported prior to the preparative regimen for the subsequent HCT/GT, to capture any events that occurred in between.

Best Response

This section should be completed only for Day 100 and 6 Months follow-up and will be disabled for all subsequent reporting periods for online data entry in EBMT Registry. This section is not applicable for Inborn Errors and can be skipped.

Best clinical/biological response after this GT

Report the patient's best response achieved after GT but before any subsequent treatment, even if the patient got worse again afterwards. Please refer to Appendix 1 on the form to select the best response that is appropriate for the diagnosis of the patient. This includes the response observed before any subsequent treatment. If the best response after the GT has not been evaluated, select **Not evaluated**. If the best response after the GT is unknown, select **Unknown**.

The best response is often achieved in the first 100 days after GT. However, for some diseases the best response to GT may take longer and therefore shall be reported as well at 6 months.

If the patient had a relapse/progression post-GT and received 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.

Recovery

This section should be completed only for the Day 100 and 6-month follow-up. It will be disabled for all subsequent reporting periods in the EBMT Registry online data entry system. If recovery occurred by Day 100, the 6-month follow-up report can be skipped.

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 0.5×10^9 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 [Date of the last assessment](#)) if:

- The stem cell source is either PB or BM and the ANC $< 0.5 \times 10^9$ cells/L,
- The stem cell source is CB and the ANC $< 0.5 \times 10^9$ cells/L

Answer **Yes** if the absolute count of neutrophils post-GT is higher or equal to 0.5×10^9 cells/L for 3 laboratory values (and proceed to [Date of ANC recovery](#)).

If the absolute count of the patient's neutrophils was never below 0.5×10^9 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 known post-GT and as **Not evaluated** if it was not assessed.

Date of the last assessment

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

Date of ANC recovery

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

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 [Date of the last assessment](#)) 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 [Date of platelet reconstitution](#)) 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 20×10^9 cells/L at any time post-GT and a platelet transfusion was never required. If the recipient's platelet count drops below 20×10^9 cells/L and/or the recipient received a platelet transfusion even once, do not use this option.

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

Date of the last assessment

Indicate the date of the last assessment of the patient's platelets level, or if not known mark the date as **Unknown**.

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 **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.

Date of the last platelet transfusion

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

Therapy Success (only for Primary Immunodeficiencies)

Engraftment of the modified stem cells assessed?

Answer **Yes** if successful engraftment of the modified stem cells is observed. Answer **No** if it is not observed. If the engraftment of the modified stem cells has not been assessed, please select **Not evaluated**.

Date evaluated

Report the date when the engraftment of the modified stem cells was evaluated, or mark as **Unknown** if the date is not known.

Engraftment of the modified stem cells - Description

Report all the cell types analysed for this engraftment assessment from the following list of cell types:

- T cells
- B cells
- NK cells
- PMN
- Monocytes
- Other; specify

Vector copy number (VCN) per transduced cell

Report the Vector Copy Number (VCN) per transduced cell. Mark as **Unknown** if the VCN is not known, or **Not evaluated** if the VCN hasn't been assessed for this cell type.

Note: VCN applies only to gene transfer gene therapy.

Gene editing efficiency

Indicate the percentage of gene editing efficiency for each of the cell types. Mark as **Unknown**, if the respective percentage is not known, or **Not evaluated** if the gene editing efficiency wasn't evaluated.

Note: Gene editing efficiency applies only to gene editing Gene therapy.

Therapy Success (only for Haemoglobinopathies)

Vector copy number (VCN) (for gene transfer Gene Therapy only)

For gene transfer Gene Therapy only, report the vector copy number.

Gene-edited cells (for gene editing Gene Therapy only)

For gene editing type of Gene Therapy only, report the percentage of the gene-edited cells.

HbF (for gene editing Gene Therapy only)

For gene editing type of Gene Therapy only, report the expression of fetal haemoglobin (HbF) percentage, or mark the field as **Not evaluated** or **Unknown**.

HbS (for sickle cell disease only)

For sickle cell disease only, report the expression of Sickle haemoglobin (HbS) percentage, or mark the field as **Not evaluated** or **Unknown**.

H87q (for Bluebird Bio product only)

For Bluebird Bio product only, report the expression of H87q percentage, or mark the field as **Not evaluated** or **Unknown**.

Other therapy specific recovery; specify

Specify data as to any other than reported above therapy specific recovery by adding it in the Specify text field in English.

Current Haematological Findings

Haemoglobin

Report haemoglobin level in g/dL or mark it as **Not evaluated** or **Unknown**.

Ferritin

Report ferritin level in ng/mL or mark it as **Not evaluated** or **Unknown**.

Extended dataset

Antimicrobial prophylaxis

Did the patient receive antimicrobial prophylaxis?

Indicate if the patient received any type of prophylaxis.

If yes, what type of prophylaxis?

Check all types of prophylaxis the patient received.

Antibacterial

Antibiotics

Check all types of antibiotics that were administered as prophylaxis.

Phase

Only for the Day 100 Follow-Up:

Select the phases (**pre-engraftment**, **post-engraftment**) during which the antibiotic was administered.

If administered during the post-engraftment phase, indicate whether it was given only during post-engraftment, or whether it was a continuation from pre-engraftment into post-engraftment, or stopped during pre-engraftment and then restarted during post-engraftment. Select **unknown** if you do not know during what phase(s) the antibiotic was given.

For Follow-Ups after Day 100:

Indicate whether the antibacterial prophylaxis was **started during this follow-up period**, or whether it is a **continuation from the previous follow-up period**. If started during this follow-up period, indicate the start date or select **unknown** if you do not know the start date.

Final date the antibacterial prophylaxis was discontinued

Report the date the patient last received any type of antibacterial prophylaxis, or select **unknown** if you do not know the final date antibacterial prophylaxis was administered, or select **ongoing** if the patient is still receiving antibacterial prophylaxis.

Antiviral

Did the patient receive cytomegalovirus (CMV) prophylaxis during this follow-up period?

Indicate if any type of CMV prophylaxis has been administered.

Which drugs were used?

Check all types of drugs that have been administered as CMV prophylaxis.

Final date CMV prophylaxis was discontinued

Report the date the patient last received any type of CMV prophylaxis, or select **unknown** if you do not know the final date CMV prophylaxis was administered, or select **ongoing** if the patient is still receiving any type of CMV prophylaxis.

Did the patient receive prophylaxis for varicella-zoster virus (VZV) or /herpes simplex virus (HSV) with either acyclovir or valacyclovir during this follow-up period?

Indicate if either acyclovir or valacyclovir has been administered as VZV or HSV prophylaxis.

Final date VZV or /HSV prophylaxis was discontinued

Report the date the patient last received either acyclovir or valacyclovir as VZV or HSV prophylaxis, or select **unknown** if you do not know the final date either acyclovir or valacyclovir was last administered as VZV or HSV prophylaxis, or select **ongoing** if the patient is still receiving either acyclovir or valacyclovir as VZV or HSV prophylaxis.

Did the patient receive rituximab or another anti-CD20 monoclonal drug as prophylaxis for Epstein-Barr virus post-transplant lymphoproliferative disorder (EBV-PTLD) during this follow-up period?

Indicate if any anti-CD20 monoclonal drug, including rituximab, has been administered as EBV-PTLD prophylaxis.

Did the patient receive prophylaxis for hepatitis B (HBV) during this follow-up period?

Indicate if any type of HBV prophylaxis has been administered.

Which drugs were used?

Check all types of drugs that have been administered as HBV prophylaxis.

Final date HBV prophylaxis was discontinued

Report the date the patient last received any type of HBV prophylaxis, or select **unknown** if you do not know the final date HBV prophylaxis was administered, or select **ongoing** if the patient is still receiving any type of HBV prophylaxis.

Antifungal

Antifungal

Check all types of antifungals that have been administered as prophylaxis.

Phase

Only for the Day 100 Follow-Up:

Select the phases (**pre-engraftment**, **post-engraftment**) during which the antifungal was administered. If administered during the post-engraftment phase, indicate whether it was given only during post-engraftment, or whether it was a continuation from pre-engraftment into post-engraftment, or stopped during pre-engraftment and then restarted during post-engraftment. Select **unknown** if you do not know during what phase(s) the antifungal was given.

For Follow-Ups after Day 100:

Indicate whether the antifungal prophylaxis was **started during this follow-up period**, or whether it is a **continuation from the previous follow-up period**. If started during this follow-up period, indicate the start date or select **unknown** if you do not know the start date.

Final date the antifungal prophylaxis was discontinued

Report the date the patient last received any type of antifungal prophylaxis, or select **unknown** if you do not know the final date antifungal prophylaxis was administered, or select **ongoing** if the patient is still receiving antifungal prophylaxis.

Did the patient receive prophylaxis for *Pneumocystis jirovecii* pneumonia (PJP) during this follow-up period?

Indicate if any type of PJP prophylaxis has been administered.

Which drugs were used?

Check all types of drugs that have been administered as PJP prophylaxis.

Final date prophylaxis was discontinued

Report the date the patient last received any type of PJP prophylaxis, or select **unknown** if you do not know the final date PJP prophylaxis was administered, or select **ongoing** if the patient is still receiving PJP prophylaxis.

Pre-emptive viral therapy

Did the patient receive pre-emptive therapy for a viral infection during this follow-up period?

Indicate if the patient received pre-emptive therapy for any virus.

If yes, for what virus?

Indicate whether the patient has received pre-emptive therapy for CMV and/or EBV.

Specify the pre-emptive therapy for each CMV episode that occurred during this follow-up period

Repeat the questions below for each CMV episode to reflect all episodes that occurred.

CMV treatment start date

Report the date the patient first received any type of pre-emptive therapy for CMV, or select **unknown** if you do not know the date.

Antiviral(s) used

Check all types of antivirals that have been administered as pre-emptive therapy for CMV.

Was this episode of CMV infection due to a resistant CMV strain?

Indicate if the CMV strain causing this CMV episode was identified to be of a drug-resistant phenotype with viral genetic mutations decreasing susceptibility to one or more antiviral drugs, or select **unknown** if you do not know if it was a resistant CMV strain.

Specify the pre-emptive therapy for each EBV episode that occurred during this follow-up period

Repeat the questions below for each EBV episode to reflect all episodes that occurred.

EBV treatment start date

Report the date the patient first received any type of pre-emptive therapy for EBV, or select unknown if you do not know the date.

Antiviral(s) used

Check all types of antivirals that have been administered as pre-emptive therapy for EBV.

Complications Since The Last Report - Non-Infectious Complications

Do not report complications that were resolved before this gene therapy.

Do not report complications that were previously reported as resolved, unless they recurred.

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

If no other non-infectious complication than GvHD occurred during the follow-up period or if the complication was grade 1 or 2, select **No** and proceed to the next section. If non-infectious complications with a CTCAE grade of at least 3 occurred, select **Yes** and report in the table below.

If the status of the adverse event is unknown, select **Unknown**.

For adverse events not listed in the table, specify them in the **Other** text field. Consult with Appendix 4 in the paper form which non-infectious complications should not be reported even for grades 3 and 4.

If a grading is dependent on hospitalisation but the patient was an inpatient at the time of onset, the centre will make the interpretation. If the patient had been an out-patient and the severity was such that the patient would have been hospitalised, grading will be selected accordingly.

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. Please note that if an event can be reported in more than one type of adverse event, it should be reported only once in the most precise category.

If the adverse event was diagnosed and reported in a previous reporting period, and the symptoms continue into this reporting period, indicate **Yes** and provide the details in the following questions.

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 grade observed during this follow-up period

Select for each adverse event the maximum grade that was observed in the reporting period. If the grade is unknown, select **Unknown**. If not otherwise specified, CTCAE grading system is to be used.

Onset date

Report the onset date when the adverse event was first observed during this follow-up period. If the complication is ongoing since the previous assessment this question will be disabled.

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.

Complications since the last report - Infectious complications

Did infectious complications occur during the follow-up period?

Answer **Yes** if any infectious complications occurred during this follow-up period.

Infections already reported on the previous follow-up need to be reported again if they were ongoing at the previous follow-up and thus continued into this follow-up. In this case, please update the information (e.g. clinical implications/localization/resolution) if any changes have occurred.

Infections already resolved at the previous follow-up do not need to be reported, unless a reactivation occurred.

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 hospitalisation
- 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)
- Positive culture without clinical implications (i.e. symptoms/signs of disease; administration of pathogen-directed therapy; isolation precautions or surveillance).

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.

New or ongoing

Indicate if the patient had a **Newly developed** bacterial infection or if it was **Ongoing since previous assessment**.

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 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.

If the start date was already reported on the previous follow-up form (with the **Ongoing since the previous assessment** option selected), the start date does not need to be reported again.

Type of bacteria

Select the type of bacteria by marking if it is 'Gram-positive', 'Gram-negative' or 'Other' (see the list in Appendix 2 of the form or available in the database).

Pathogen

Select the bacterium that caused the infection from the list in Appendix 2 of the form or available in the database. Choose the most specific option. If the pathogen cannot be found, choose the 'Gram-positive bacteria other spp', 'Gram-negative bacteria other spp' or 'Bacteria 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. If relevant susceptibility data is unavailable, 'Gram-positive bacteria other spp' or 'Gram-negative bacteria other spp' can be selected (e.g. in case of *Pseudomonas* without information on carbapenem susceptibility (meropenem, imipenem or doripenem) choose 'Gram-negative bacteria other spp'). For *Staphylococcus aureus*: if vancomycin susceptibility is unavailable, but it is methicillin-susceptible (can appear as "oxacillin"), it should be reported as '*Staphylococcus aureus* MSSA (methicillin-susceptible)'. For '*Staphylococcus aureus* MRSA (methicillin-resistant)', indicate

whether the vancomycin susceptibility was not tested, or whether it was VISA (vancomycin-intermediate) or VRSA (vancomycin-resistant) based on the minimum inhibitory concentration (MIC) for vancomycin falling within the range noted in the Appendix.

Common commensals (most commonly coagulase-negative Staphylococci, *Micrococcus* spp., *Bacillus* spp., *Propionibacterium* spp.) should be reported only if there are at least two positive blood cultures.

Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark **Unknown** if it is not possible to identify. Infection with clinical implications is at least one of the following: symptomatic infection in the relevant organ/system, or infection that requires pathogen-directed therapy.

Infection with clinical implications, yes:

Select all clinical implications of the infection during this follow-up period that apply from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;

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 at least 1 location involved during this follow-up period 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).

If the clinical information available doesn't specify the localisation of the infection, probably the infection was asymptomatic and will not have to be reported. Otherwise, the symptoms should guide the choice.

Intravascular catheter-related infection

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

- The same organism (genus, species, and susceptibility pattern) growing from at least 1 percutaneous blood sample culture and from the catheter tip (e.g. two coagulase-negative Staphylococci, but different species, such as *Staphylococcus capitis* and *Staphylococcus*

epidermidis, or two *Staphylococcus epidermidis* with completely different susceptibilities are not the same).

- 2 blood samples for culture are obtained (1 from a catheter hub and 1 from a peripheral vein) that meet CVC-related bacteraemia 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 (9).

Specify

If the infection was related to an intravascular catheter, select the type of CVC infection from the list in Appendix 4 or available in the database.

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.

Contributory cause of death

In case the patient is deceased, indicate if the infection contributed to death.

If there was more than one bacterial infectious complication during the follow-up period, repeat these questions for the subsequent infection. Copy and fill-in the table as many times as necessary.

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.

New or ongoing

Indicate if the patient had a **Newly developed** viral infection or if it was **Ongoing since previous assessment**.

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.

In case the start date was already reported on the previous follow-up form (with the **Ongoing since previous assessment** option selected), the start date does not need to be reported again.

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 'Viruses other' option and enter its name in a textbox. Always report the full name of the virus.

If the pathogen was CMV/EBV: was this infection a reactivation?

Answer yes, if the patient's serology tests (CMV IgG, EBNA, EBV IgG) were positive before the treatment (start of lymphodepleting/conditioning regimen) took place, or if the patient has been reported to have previously had an active CMV/EBV infection.

Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark **Unknown** if it is not possible to identify. Infection with clinical implications is at least one of the following: symptomatic infection in the relevant organ/system, or infection that requires pathogen-directed therapy.

Infection with clinical implications, yes

Select all clinical implications of the infection during this follow-up period that apply:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;

Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 3 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 at least 1 location during this follow-up period 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).

If the clinical information available doesn't specify the localisation of the infection, probably the infection was asymptomatic and will not have to be reported. Otherwise, the symptoms should guide the choice.

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.

Contributory cause of death

In case the patient is deceased, indicate if the infection contributed to death.

If there was more than one viral infectious complication during the follow-up period, repeat these questions for the subsequent infection. Copy and fill-in the table as many times as necessary.

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.

New or ongoing

Indicate if the patient had a **Newly developed** bacterial infection or if it was **Ongoing since previous assessment**.

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.

In case the start date was already reported on the previous follow-up form (with the **Ongoing since previous assessment** option selected), the start date does not need to be reported again.

Type of fungi

Select the type of fungal infection by marking if it is 'Yeasts' or 'Moulds'.

Pathogen

Select the fungus that caused the infection from the list in Appendix 2 of the form or available in the database. Choose the most specific option. If the pathogen cannot be found, choose the 'Yeasts other' or 'Moulds 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.

Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark unknown if it is not possible to identify. Infection with clinical implications is at least one of the following: symptomatic infection in the relevant organ/system, or infection that requires pathogen-directed therapy.

Infection with clinical implications, yes

Select all clinical implications of the infection during this follow-up period that apply from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;

Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 3 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 at least 1 location during this follow-up period 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).

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 (genus, species and susceptibility pattern) 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 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 (9).

Specify

If the infection was related to an intravascular catheter, select the type of CVC infection from the list in Appendix 4 or available in the database.

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.

Contributory cause of death

In case the patient is deceased, indicate if the infection contributed to death.

If there was more than one fungal infectious complication during the follow-up period, repeat these questions for the subsequent infection. Copy and fill-in this table as many times as necessary.

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.

New or ongoing

Indicate if the patient had a Newly developed parasitic infection or if it was **Ongoing since previous assessment**.

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.

In case the start date was already reported on the previous follow-up form (with the **Ongoing since previous assessment** option selected), the start date does not need to be reported again.

Type of parasite

Select the type of parasitic infection by marking if it is 'Protozoa' or 'Helminths'.

Pathogen

Select the parasite that caused the infection from the list in Appendix 2 of the form or available in the database. Choose the most specific option. If the pathogen cannot be found, choose the 'Protozoa other spp' or 'Other helminths' option and enter its name in a textbox. Always report the full name of the parasite.

Infection with clinical implications

Indicate if the infection had clinical implications or not, or mark unknown if it is not possible to identify. Infection with clinical implications is at least one of the following: symptomatic infection in the relevant organ/system, or infection that requires pathogen-directed therapy.

Infection with clinical implications, yes

Select all clinical implications of the infection during this follow-up period that apply from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;

Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 3 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 at least 1 location during this follow-up period 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).

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.

Contributory cause of death

In case the patient is deceased, indicate if the infection contributed to death.

If there was more than one parasitic infectious complication during the follow-up period, repeat these questions for the subsequent infection. Copy and fill-in this table as many times as necessary.

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, typhlitis, etc.

New or ongoing

Indicate if the patient had a **Newly developed** infection with unknown pathogen or if it was **Ongoing since previous assessment**.

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.

In case the start date was already reported on the previous follow-up form (with the **Ongoing since previous assessment** option selected), the start date does not need to be reported again.

Infection with clinical implications

Infection with clinical implications is at least one of the following: symptomatic infection in the relevant organ/system, or infection that requires pathogen-directed therapy. Since an infection with an unknown pathogen always has clinical implications to be reported, the 'Infection with clinical implications, yes' field always has to be filled in.

Infection with clinical implications, yes

Select all clinical implications of the infection during this follow-up period that apply from suggested answer options:

- Symptoms/signs of disease;
- Administration of pathogen-directed therapy;

Localisation (CTCAE term)

Select the CTCAE term for the infection from the list in Appendix 3 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 at least 1 location during this follow-up period 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).

If an infectious complication with an unknown pathogen occurred and the localisation cannot be identified or is uncertain, diagnosis may be febrile neutropenia or fever (there is such a CTCAE term) since sepsis or bacteremia cannot be diagnosed without an organism.

If the clinical information available doesn't specify the localisation of the infection, probably the infection was asymptomatic and will not have to be reported. Otherwise, the symptoms should guide the choice.

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.

Specify

If the infection was related to an intravascular catheter, select the type of CVC infection from the list in Appendix 4 or available in the database.

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.

Contributory cause of death

In case the patient is deceased, indicate if the infection contributed to death.

If there was more than one infectious complication with an unknown pathogen during the follow-up period, repeat these questions for the subsequent infection. Copy and fill-in this table as many times as necessary.

Extended dataset

SARS-CoV-2 related question

Did the patient receive a vaccination against SARS-CoV-2 during this follow-up period?

Indicate if the patient received a vaccination against SARS-CoV-2 in the follow-up period after the GT treatment took place.

Number of doses

Report how many doses of the SARS-CoV-2 vaccine the patient has received.

Date of last dose

Report the date on which the patient received their last dose of the SARS-CoV-2 vaccine

Secondary Malignancies and Autoimmune Disorders

Did a secondary malignancy or autoimmune disorder occur?

Answer **No** if no secondary malignancy or autoimmune disorder occurred or if the secondary malignancy or autoimmune disorder was already reported in the previous GT follow-up form.

Answer **Yes** if secondary malignancy or autoimmune disorder occurred and it has not been reported with a GT follow-up form yet. The secondary malignancy can be any disease for which the patient had not been diagnosed before the GT. Do not include relapse, progression or transformation of the same disease subtype.

If secondary malignancy or autoimmune disorder answered Yes, provide further details on secondary malignancy or autoimmune disorder in the next questions.

Diagnosis

Specify the diagnosis of secondary malignancy/autoimmune disorder.

Date of diagnosis

Report the date of diagnosis of secondary malignancy/autoimmune disorder.

Histologic type

If applicable, report the histologic type.

Location

If applicable, report where the secondary malignancy or autoimmune disorder occurred.

Secondary malignancy material preserved

Answer **Yes** if secondary malignancy material was preserved. Answer **No** if secondary malignancy material was not preserved. If it is not known if secondary malignancy material was preserved or not, select **Unknown**.

Concomitant PBMCs preserved

Answer **Yes** if concomitant peripheral blood mononuclear cells (PBMCs) were preserved. Answer **No** if concomitant PBMCs were not preserved. If it is not known if concomitant PBMCs were preserved or not, select **Unknown**.

Viral vectors: Did insertional mutagenesis occur

Answer **Yes** and provide further details in subsequent questions if insertional mutagenesis occurred in the follow up period.

Answer **No** if insertional mutagenesis did not occur in the follow up period or if it was reported in the previous follow up report.

Otherwise mark this question as **Not evaluated** or **Unknown**, whatever is a more applicable answer option.

Note: This question applies only to gene transfer type Gene Therapy.

Integration site; specify

If insertional mutagenesis occurred, specify the integration site, or mark it as **Not evaluated** or **Unknown**.

Integration site clonal diversity

If insertional mutagenesis occurred, specify the integration site clonal diversity according to Shannon diversity index by selecting one of the answer options:

- Very High;
- High;
- Moderate;
- Low;
- Very Low;
- Not evaluated;
- Unknown.

Additional Cell Infusions

Did the patient receive an (salvage infusion) autologous boost?

Answer **Yes** if the patient received an autologous boost immediately after this gene therapy or since the last follow-up. This autologous boost describes the re-infusion of previously stored autologous stem cells of the patient to salvage the patient from non-engraftment (lead to aplasia).

Answer **No**, if the patient did not receive an autologous boost immediately after this gene therapy or since the last follow-up.

Date of the (salvage infusion) autologous boost

If the answer to the previous question is **Yes**, please provide the date of the autologous boost administration. Answer **Unknown** if this date is unavailable.

Recurrence of disease

Was there a recurrence of disease since last follow-up?

For Haemoglobinopathies indicate if there was a recurrence the primary disease after GT detected by any method. If multiple instances of recurrence of disease took place in this follow-up period, report all instances. ('+ Add' on the EBMT Registry.) If the answer is **No**, proceed to the next section. For Inborn Errors this question is not applicable and will be disabled.

Date of recurrence

Report the date of the recurrence since GT. If the date is not known, select **Unknown**.

Hospital Admission

Complete this section only for Day 100 and 6 Months Follow-Up.

Was inpatient admission and care needed since the last follow-up

If the patient did not require inpatient admission or care since the last follow-up, select **No** and proceed to the next question. If inpatient admission and care was needed since the last follow-up, select **Yes** and report the **number of days the patient was admitted in the hospital**.

If it is unknown if inpatient admission and care was needed since the last-follow up, select **Unknown**.

Was the patient transferred to the intensive care unit (ICU) since the last follow-up

If the patient was not transferred to the ICU since the last follow-up, select **No**. If the patient was transferred to the ICU after the last follow-up, select **Yes** and report the **number of days the patient spent in the ICU**.

If it is not known whether the patient was transferred to ICU or not since the last follow-up, select **Unknown**.

Patient Status

Performance status at the last assessment

Select one answer to indicate the performance score system used to calculate the performance status at gene therapy follow-up:

- **Karnofsky;**
- **Lansky;**
- **ECOG.**

Report the score that reflects the performance status at the current follow-up. It is not necessary to fill in both the Karnofsky/Lansky and ECOG score, one is sufficient. Descriptions of the Karnofsky score system can be found in table 1 below, Lansky in table 2 and the ECOG score system can be found in table 3 below.

Karnofsky scale

Score	Performance Status
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	HospitalisationHospitalization indicated, although death not imminent; severely disabled
20	HospitalisationHospitalization necessary; active supportive treatment required, very sick
10	Fatal processes progressing rapidly; moribund
0	Dead

Table 1. Karnofsky scoring system for adult patients

Lansky scale

Score	Performance Status
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

Table 2. Lansky scoring system for paediatric patients

ECOG scale

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Table 3. ECOG scoring system

Disease Status - Disease specific

Disease status at this follow-up or at time of death

Indicate the disease status at this follow-up or at time of death corresponding to indication diagnosis by selecting from the list provided in Appendix 1.

The disease status is split into disease specific sections:

- Haemoglobinopathies
- Other diagnoses

The instructions for completing appendix 1 can be found in appendix 1 of this document.

Pregnancy after gene therapy

Complete for every follow-up after 6 Months post gene therapy.

Has a patient become pregnant or impregnated another person since the last follow-up?

If the patient has not become pregnant or has not impregnated another person since the last follow-up, select **No** and proceed to the next section.

Extended dataset

Indicate if there was an attempted pregnancy since the last follow-up select **Yes, No or Unknown**.

If the patient has become pregnant or has impregnated another person since the last follow-up select **Yes** and provide details in the subsequent question below. Select **Unknown** if it is not known.

Did the pregnancy result in a live birth?

If the patient has become pregnant or has impregnated another person since the last follow-up, answer **Yes**. If the pregnancy resulted in a live birth, indicate the **Year of birth** and **Month of birth** of the child, or mark the date **Unknown** if the date is not available.

Answer **No** if pregnancy did not result in a live birth and indicate the **Date of spontaneous or induced termination** (YYYY/MM/DD) or mark the date as **Unknown**. In case of multiple spontaneous or induced terminations, report the date of the first such event.

Select **Still pregnant at time of follow-up** if the patient/the person they impregnated was still pregnant at the time of the follow-up.

Extended dataset

Indicate which conception method they used. Either **Natural, Assisted** or **Unknown**

If there is no detailed information about the pregnancy and whether or not it resulted in a live birth, select **Unknown**.

If multiple pregnancies occurred in the follow-up period, the live birth should be prioritised in reporting, in the absence of the live birth, ongoing pregnancy should be prioritised: if one pregnancy resulted in live birth and another not, report the live birth only; if there occurred any terminated pregnancy and the other pregnancy is ongoing as of this follow-up date, select *Still pregnant at time of follow-up* answer option.

End Of General Follow-Up Reporting

Appendix 1 - Disease specific best response and disease status

Extended dataset

Immunomodulatory treatments (Inborn errors only)

Select the immunomodulatory treatments the patient received in the 3 months before the follow-up

Only report treatments administered in the 3 months before this follow-up for the underlying disease.

Patient status post GT

Patient height

For Day 100 follow-up report the patient height within 100 days after GT in centimetres.

For follow-up after Day 100 report the height of the patient at the last follow-up in centimetres.

Patient weight

For Day 100 follow-up report the patient weight within 100 days after GT in kilograms.

For follow-up after Day 100 report the weight of the patient at the last follow-up in kilograms.

Patient is attending

Please select whether one of the situation below applies to the patient:

Regular school/work: If the patient attending regular school or work

Alternative school/adapted work: If the patient attending school or working that is adapted to their inabilities

Patient is not able to attend work/school: if the patient does not attend school or work

If the patient is not known whether he/she is attending school or working, please select **Unknown**

Immune profiling done during this follow-up period

Indicate if immune profiling was done during this follow-up period.

Test date

Report the date of the most recent immune reconstitution was tested

Cell type and test results

Please report the value of the cell types below from the most recent test performed. For Naive CD4 T-cells and CD8 T-cells please select the unit of measurements.

Cell type	Unit of measurement
T-cells (CD3)	Cells/ μ l
CD4 T-cells (CD4)	Cells/ μ l
CD4 T-cells (CD8)	Cells/ μ l
B-cells (CD19)	Cells/ μ l
NK-cells (CD16/CD56)	Cells/ μ l
Naive CD4 T-cells (CD4/CD45RA)	Please select the unit of measurement
Naive CD8 T-cells (CD8/CD45RA)	Please select the unit of measurement
IgG	Gram/l
IgA	Gram/l
IgM	Gram/l

Patient status post GT (Inborn errors of immunity only)

Indicate if the comorbidities de novo, resolved, improved, stabilised or worsened since the last treatment took place.

Was the patient admitted to ICU during this follow-up period?

Indicate if the patient was admitted to ICU after GT. If the information is not available mark as **Unknown**.

Haemoglobinopathies

Thalassemia disease status

Patient requires regular transfusions during follow-up period

Indicate if the patient requires transfusions during follow-up period by selecting **No** or **Yes**. For clarification, patient receives non-occasional transfusions due to haemoglobin deficiency (recurrence of disease) and have not reached transfusion independence (haemoglobin (Hb) level remains at or above 9 g/dL for at least one year after gene therapy without additional transfusions).

Occasional transfusion during follow-up period

If a patient is not transfusion-dependent, indicate whether there have been occasional transfusions during this follow-up period.

Number of Units

If **Yes**, report the number of transfusion units patient received during this follow-up period. If the exact number is not known, select **Unknown**.

Reason

If **Yes**, please specify the reason for receiving transfusions. For example: acute blood loss (traumatic injury, surgical complication), infection, nutritional deficiencies.

Patient requires regular transfusions, Yes

If a patient is transfusion dependent indicate whether at this follow-up period the **Return to transfusion dependence after GT or transfusion free period** occurred or patient **Ongoing transfusion dependence since previous assessment**.

Date of first transfusion

If a patient has returned to transfusion dependence after main treatment or transfusion free period during this follow-up period, report the date of the first transfusion after main treatment or transfusion free period. If the date is not known, select **Unknown**. If a patient has ongoing transfusion dependence since the previous assessment and the date was reported at the previous follow-up form, do not report the date here, the question will be disabled.

Number of units

Report the number of transfusion units patient received during this follow-up period. If the exact number is not known, select **Unknown**.

Did transfusions stop?

Indicate if the patient stopped receiving the transfusions. If the patient stopped transfusions and did not require more during this follow-up period, select **Yes**.

Date of last transfusion

If the patient stopped transfusions during the reporting period, provide the date when the last transfusion was administered. If it is not known, select **Unknown**.

Sickle cell disease best response

Select the best response that was achieved since the main treatment:

- No return of sickling episodes. Patients are considered to have no return of sickling episodes when they have shown an absence of recurrent sickle cell crises.
- Return of sickling episodes. When recurrent sickle cell crises reoccur.

If the best response is not known or was not evaluated, select **unknown** or **not evaluated**, respectively.

Sickling episodes occur during follow-up period

For patients with Sickle cell disease only report the following:

Answer **No** if sickling episodes did not occur during the follow up period.

Answer **Yes** if sickling episodes occurred during the follow up period. In addition, please add the **Date of first episode** and **Number of SCD episodes** after gene therapy or mark the date and the number of episodes as **Unknown**.

Answer **Unknown** if there is no information on the occurrence of sickling episodes.

Other diagnosis

Disease status or best response

Select the disease status or best response from the list:

- **No evidence of disease-** the patient has achieved complete absence of disease, there are no signs or symptoms of the original disease described.
- **Improved**
- **Unchanged-** Patients who have not demonstrated complete absence of disease, improvement in symptoms, or deterioration of symptoms will be classified as **Unchanged**.
- **Worse**

If the disease status or best response is not known or was not evaluated, select **unknown** or **not evaluated**, respectively.