EBMT Registry

Autologous Hematopoietic Gene Therapy form

Day 0

Guide to the completion v1.2 of the EBMT data collection form:

GT_Day0_v1.2

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EBMT Registry

EBMT Clinical Research & Registry Department

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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.

For patients whose registration needs to be hidden, please enter into the EBMT Registry the embargo end date by following the next steps:

1. Open the patient in the EBMT Registry
2. Enter the patient menu section 'Edit patient details'.
3. Enter the Embargo end date into the dedicated data field.

The patient will become visible for the EBMT studies and analysis automatically after the embargo period ends. More details on embargo functionality in the EBMT Registry can be found in the EBMT Registry User Manual for Data Editors and Data Viewers.

Autologous Hematopoietic Gene Therapy

The Autologous Hematopoietic Gene Therapy (GT) Day 0 form should be filled and submitted online in the EBMT Registry database straight after the Gene Therapy infusion. If the GT product was not infused for whatever reason, this form still shall be submitted to record such failed events. In the context of EBMT Registry, the terms 'autologous hematopoietic gene therapy', 'gene therapy' and GT are used as synonyms and represent the same type of treatment.

The GT Day 0 form includes the following main sections:

1. Pre-infusion, that covers details about the planned treatment and the planned gene therapy product(s).
2. Gene therapy, that covers the patient's status at gene therapy including details about the gene therapy infusion unit(s).

Autologous hematopoietic gene therapy involves introducing nucleic acids (DNA or RNA) into hematopoietic stem cells for therapeutic purposes. This therapy aims to add a new copy of a "healthy" gene (additive gene therapy), disrupt a targeted gene, or correct mutated gene (gene editing).

Unlike CAR-T cell therapy, which reengineers T-cells with a different receptor for immune therapy and does not require conditioning, gene therapy modifies autologous stem cells and requires conditioning for engraftment.

In other words, gene therapy serves as a substitute therapy to restore a missing function in the body and is primarily used for patients with Inborn Errors and Haemoglobinopathies.

Gene therapy products can be infused individually, sequentially or in combination with other treatments, including HCT.

Cellular therapy (including CAR-T) should **not** be reported through this form.

Additionally, the following definitions are important:

- Gene therapy treatment is the infusion of one or more units with one indication as selected on the form as part of the planned treatment protocol, where the total units infused are not separated by additional preparative regimen/lymphodepletion.
- Gene therapy infusion unit: an infusion unit is a product consisting of one or more bags with the same type of manipulated cells with a unique batch or product number. If different manipulated cell types were used or there are different identification codes for multiple bags, these are regarded as different infusion units.
- Gene therapy infusion products: the infusion of one or more units can be done in one or over different days. If the gene therapy infusion units were infused over multiple days without additional preparative/lymphodepletion after the first infusion day, this is regarded as multiple infusion products.

Pre-infusion

Indication diagnosis for this gene therapy

At this moment, the only gene therapies that are available are gene therapies to treat primary diseases. Please enter the main indication diagnosis for this gene therapy. Make sure the indication diagnosis has been registered in EBMT Registry first, using the relevant indication diagnosis form.

During online data entry the indication diagnosis must be selected from the drop down list of all registered indication diagnoses for this patient.

Basic information on the planned gene therapy

Setting

Choose the answer option that describes the clinical setting for the planned GT.

Early access - Select this option if the patient received a gene therapy before full approval, under national rules, usually when no other treatment is available.

As per market authorisation / Standard of care / Institutional guidelines - Select this option if the patient is treated with a marketed gene therapy product, according to the centre's standard of care policies and institutional guidelines.

Accelerated access - Select this option if the patient is treated under compassionate use. These are regulatory provisions under which a gene product can be administered to a specific patient outside of a clinical trial, upon request and approval from regulatory agencies. Regulations may vary from country to country and some countries may not provide such opportunities. In case of doubt, please check with a clinician in the treating centre.

Investigational drug product (IDP) / Clinical trial - Select this option if the patient is enrolled in a clinical trial, whether academic-sponsored or industry-sponsored. If the product was administered in a clinical trial setting or as an investigational product, answer also the following questions.

Phase

Indicate the phase of the IDP or clinical trial by marking if it is:

- 1;
- 1/2;
- 2;
- 2/3;
- 3

Randomised trial

Answer **Yes** if the treatment is allocated randomly to the trial subjects, otherwise answer **No**.

Trial number (select all that apply)

Trial number is a unique identifier assigned to a particular clinical trial. Various trial numbers may be applicable based on different regulatory bodies and trial registration systems.

EudraCT number

The EudraCT number is assigned to trials conducted within the EU and serves as a standardised identifier for these trials. Indicate the number given to the trial when registered with the European Clinical Trials Database.

USA NCT number

The USA NCT number is assigned to trials conducted in the United States. Indicate the clinical trial number (NCT number). If the number is not clearly documented, it can be found using the 'Find a Study' feature on www.clinicaltrials.gov.

UMIN CT number

Japanese clinical trials number, only applicable to trials (also) conducted in Japan.

Planned gene therapy infusion product(s)

Is the planned cell infusion product a commercial product?

If the product was made by the hospital or administered before market authorization, the product is not commercial and this question should be answered **No**. If the product is manufactured by a pharmaceutical company after market authorization was obtained, the product is considered to be a commercial product and it should be answered **Yes**.

Report below the Identification details of the planned gene infusion product.

Identification

Report below the Identification details of the planned gene infusion product.

Name of manufacturer / Marketing authorisation holder

Select the name or type of the facility which manufactured the infusion product (pharmaceutical or biotech company, cell processing laboratory or another site) out of the following options:

- **Aruvant Sciences**
- **Appelis Pharmaceuticals**
- **AvroBio**
- **Beam Therapeutics**
- **Bluebird Bio**
- **CRISPR Therapeutics**
- **Editas Medicine**

- **Graphite Bio**
- **Mustang Bio**
- **Orchard Therapeutics**
- **Rocket Pharmaceuticals**
- **Genenta Science**
- **Telethon foundation**
- **Vertex**

If no answer from the list is applicable, select **Other** and specify the name in the text box in English.

Product name

Select the product name out of the following options:

- **Libmeldy** (Atidarsagene autotemcel);
- **Zynteglo** (Betibeglogene autotemcel);
- **Skysona** (Elivaldogene autotemcel);
- **Casgevy** (Exagamglogene autotemcel);
- **Strimvelis** (autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence)
- **Temferon**

If the product name is not on the list, select **Other** and specify the name in the text box.

Will the planned gene therapy infusion product consist of more than one infusion unit?

A Gene therapy infusion unit is a product consisting of one or more bags/vials with the same type of manipulated cells, with a unique batch or product number. If different manipulated cell types were used, or if there are different identification codes for multiple bags, these are regarded as different infusion units.

Answer **No** if planned gene therapy infusion product will consist of one infusion unit.

Answer **Yes** if planned gene therapy infusion product will consist of more than one infusion unit and report the **Number of infusion units**.

Mark **Unknown** if there is no information yet on the number of infusion units in the gene therapy infusion product. Please return and update this information once known.

Tissue source (check all that apply)

Select the tissue(s) from which the cells that were used for the gene therapy product were collected:

- Bone marrow;
- Peripheral blood;
- Umbilical cord blood;
- Other; specify the tissue source in the textbox.

Cell type

Select all the cell types that are in the gene therapy product:

- **CD34+** hematopoietic stem cells;
- **T-cells (other than CAR-T cells)**;
- **Other**; specify it in the text field.

Mobilisation

Note: This section should be completed for every apheresis

Mobilisation drugs given?

Indicate if the patient received mobilisation drugs prior to apheresis for the gene therapy. If the answer is **Yes**, indicate:

Start date of mobilisation

Report the start date of the mobilisation if the patient received mobilisation therapy.

G-CSF

Indicate if the patient received the following growth factor (granulocyte-colony stimulating factor) drugs by answering **Yes**. If the patient did not receive any G-CSF, answer **No** to all options:

- Filgrastim;
- Lenograstim;
- Pegfilgrastim.

Plerixafor

Indicate if the patient received plerixafor as a mobilisation drug by answering **Yes**, otherwise answer **No**.

Other mobilisation drug

Select this box if the patient received any mobilisation drug other than listed above (not G-CSF or plerixafor), report the generic name of the drug in the textbox. Please consult the LIST OF CHEMOTHERAPY DRUGS/AGENTS AND REGIMENS on the EBMT website for drugs/regimens names.

If the answer for any of these drugs is **Yes**, indicate also:

Total dose

If the patient received any mobilisation drugs, report for each drug the total dose in **mg/kg** or **mg/m^2**. If the total dose is not known, please indicate **Unknown**.

CD34+ cell count at apheresis (in peripheral blood)

If the patient received any mobilisation drugs, report the CD34+ cell count before apheresis after mobilisation in 1/mL.

Complications after mobilisation

Indicate whether the patient experienced any complications after mobilisation by answering **Yes** or **No**. If the answer is **Yes**, please also specify whether it was a sickling episode, a specified vaso-occlusive crisis, or **Other** if it was another complication. If **Other**, please specify.

Collected Cells

First date of successful collection

Report the first date of successful cell collection. Please select **Unknown** if the date is not known.

Total number of collection cycles

Indicate the total number of collection cycles. A collection cycle typically consists of harvesting cells from the patient after mobilisation, potentially containing multiple apheresis sessions on consecutive days. Select **Unknown** if the number of collection cycles is not known.

Is the exact number of collected cells available?

Answer **Yes** if the exact number of collected cells for the creation of this gene therapy product is available and complete the following three questions.

Number of cells collected

Report the total number of collected cells prior to mobilisation not adjusted for cell viability by specifying the number of cells. This number should not be corrected for cell viability.

Units

Indicate the units in which the number of cells is reported. Report the dose units as either 10^6/kg, 10^6, 10^8/kg, 10^8.

Cell viability

Indicate the cell viability percentage or select **Unknown** if this information is not known.

Was a back-up product collected?

Answer **Yes** if a back-up product was collected. If a back-up product was collected, complete the following question. If no back-up product was collected, select **No**. Answer **Unknown** if it is not known.

Was the back-up product cryopreserved?

Answer **Yes** if the back-up product was cryopreserved. If the back-up product was not cryopreserved, select **No** and select **Unknown** if it was not known if the back-up product was cryopreserved.

Previous therapies (before gene therapy)

This section collects data about treatments the patient may have received prior to this gene therapy. Do not report preparative/lymphodepleting regimen in this section.

Did the patient receive a previous HCT?

Answer **No** if the patient did not receive HCT in the past.

Answer **Yes** if the patient received HCT in the past and answer subsequent questions. Additionally, please ensure that the HCT form Day 0 (allogeneic or autologous) has been filled out if it hasn't been completed yet.

Date

Report the date of the latest HCT.

Type

Report the type of the latest HCT the patient received by marking if it was an **Autologous** or **Allogeneic** HCT**.**

For same indication as the gene therapy?

Answer **No** if the indication for the last HCT was different from the indication for the gene therapy. A same indication means for the same disease as is being treated with this gene therapy.

Answer **Yes** to mark that the indication for the gene therapy is the same as it was for the last HCT.

Gene therapy Main Treatment

Date of (planned) gene therapy infusion

Report the date the gene therapy product was infused, or the planned date of infusion if the infusion did not take place.

Important note: this date will be recorded as the date of gene therapy in the patient timeline and should be entered while creating a Gene therapy treatment event in the EBMT Registry online application.

Centre where treatment took place

Enter the Centre Identification Code (CIC) of the centre where infusion took place. If the product was not infused, report the centre where the infusion was planned to take place.

Patient UPN for this treatment

Enter the UPN of the patient at the time of this treatment.

Team or unit where treatment took place (select all that apply)

Select the team or unit where the treatment took place. Multiple options can be selected. If **Other; specify** is selected, you must give further information on the name of the team or unit where the treatment took place. For example, your team or unit name may be derived from your geographical location (e.g. south unit or north unit).

Unit number (not Other team or unit; specify)

Unit numbers have been assigned by national registries to different teams submitting data under the same CIC. This will allow data in filtered searches and exports to be team specific.

If your centre does not have separate teams with assigned unit numbers select **Not applicable**.

Was the gene therapy product infused during this treatment/procedure?

Indicate if the gene therapy product was infused. Answer **No** if the product was not infused and specify the reason in the subsequent question.

Reason why the treatment did not take place

If the product was not infused, select all the appropriate reason(s) that apply:

- **Production failure**

- **Out of specification product rejected by physician**
- **Disease progression or patient condition worsening**
- **Patient became ineligible for treatment**
- **Patient died**
- **Other reason**; specify the reason in the text box.

If no infusion took place, the data entry for this form is stopped here. The status at treatment form needs to be completed, using the date of planned infusion as treatment date.

Gene therapy infusion unit(s)

Was more than one gene therapy infusion unit administered during this treatment?

Answer **No** if the patient had only one gene therapy infusion unit during this gene therapy treatment.

If more than one gene therapy infusion unit was infused, answer **Yes** here and specify the next sub-question.

Number of different gene therapy infusion units that were part of this treatment

Specify the number of gene therapy infusion units administered during this gene therapy treatment.

This number will correspond to the number of copies of the **Gene therapy infusion unit(s)** section that needs to be filled in and submitted.

Gene Therapy Infusion Unit(s)

If more than one gene therapy infusion unit was infused, please copy and fill-in this section for each one of them. While entering the data online, please click on "+ Add Gene therapy infusion unit(s)" for each additional gene therapy infusion unit administered during this gene therapy.

Unique ID of the product

Enter the unique identification code of the product, if it is available (e.g. serial number).

Batch number

Report the batch number of the gene therapy infusion unit, if applicable.

Identification of the gene therapy infusion unit given by the centre

Report the gene therapy infusion unit identification that was assigned to the unit by the treating centre. This information is mandatory if more than one gene therapy infusion unit has been used in the same

treatment. If there is only one gene therapy infusion unit with no assigned identification number, enter '1'.

Was the infused gene therapy product consistent with the specifications?

Answer **Yes** if the product was consistent with the specifications.

Answer **No** if the product was not consistent with the specifications and specify the **difference from specifications** in the text field. Products that are out of specification did not meet the acceptance criteria set by the manufacturer.

Answer **Unknown** if it is not known if the infused cellular product is consistent with the specifications.

Consult the physician who approved the product for infusion in case of doubt.

Was this product cryopreserved prior to infusion?

Select **Yes** if the gene therapy product has been cryopreserved (frozen at very low temperatures) prior to infusion at any time point between collection and infusion. If this was not the case, select **No**. Answer **Unknown** if it is not known.

Gene Therapy Infusion Product(s): Manipulation

Complete this section only for non-commercial products.

If the infused product is a commercial product, continue with the Preparative regimen section.

If more than one gene therapy infusion unit please copy and fill-in this section for each one of them.

Identification of the gene therapy infusion unit (given by the centre)

Report the gene therapy infusion unit identification number that was assigned to the unit by the treating centre. This information is mandatory if more than one gene therapy infusion unit has been used in the same treatment. If there is only one gene therapy infusion unit with no assigned identification number, enter '1'.

Manipulation

Processing/Manufacturing facility

Indicate where the manipulation took place by choosing either:

- **Onsite, by local cell processing facility**, or

- **Offsite, by a commercial or non-commercial facility.**

Gene transfer

Gene transfer is a procedure that allows the transfer of a gene into a cell or any other organism. Answer **No** if gene transfer was not used for gene manipulation.

Answer **Yes** if gene transfer was used for gene manipulation and specify details in the subsequent questions.

Vector

Indicate the vector by choosing one of the following answer options:

- Adenoviral vector
- Adeno-associated virus (AAV)
- Lentiviral vector
- Retroviral vector
- Transposon
- Other vector; specify it in the text field.

Vector copy number (VCN)

Report the vector copy number (VCN). The VCN refers to the number of copies of a specific vector present within a population of cells. The vector is often used to deliver therapeutic genes into target cells. VCN is a critical parameter in assessing the efficiency and effectiveness of gene delivery.

Transgene

If genes were inserted, select the transgene from the following list and specify all targets:

- ABCD1
- Beta globin
- Gamma globin
- shRNA/siRNA to BCL11A
- Suicide gene; specify it in the text field
- Other; specify it in the text field

Gene editing

Gene editing is a procedure in which DNA is inserted, deleted, modified or replaced in the genome of a living organism.

Answer **Yes** if gene editing was used for gene manipulation and specify details in the subsequent questions.

Manipulation technique

Indicate the manipulation technique used for gene editing by choosing one of the following answer options:

- CRISPR-Cas9
- Transcription activator-like effector nucleases (TALEN)
- Zinc finger nucleases (ZFN)
- Other; specify it in the text field

Manipulated gene

Indicate the manipulated gene used for gene editing by choosing one of the following answer options:

- BCL11A
- Beta globin
- CCR5
- Gamma globin
- Other gene; specify it in the text field

% of the gene-edited cells

Indicate the percentage of gene-edited cells in the gene therapy infusion product.

Other

Indicate if a different genetic manipulation not previously listed (not gene transfer or gene editing) was used. If the answer is **Yes**, specify it in the text field.

Preparative regimen

Do not include lines of therapy given for disease treatment, bridging therapy or maintenance, these should be reported in other sections.

Myeloablative conditioning regimen given?

Indicate if the patient received myeloablative conditioning (MAC) chemotherapy prior to the infusion of the gene therapy product. If the answer is **Yes**, provide more details in the subsequent questions.

For each regimen used, report the total prescribed cumulative dose (total dose) as per protocol. Multiply daily dose in milligrams per kilogram or in milligrams per square metre by the number of days; e.g. for Busulfan given 4mg/kg daily for 4 days, total dose to report is 16mg/kg.

Busulfan

Indicate if the patient received busulfan as myeloablative conditioning regimen. If the answer is **Yes**, report the **total dose** in milligrams per kilogram or in milligrams per square metre and provide more details in the subsequent questions.

Route of administration

If the patient received busulfan as part of the myeloablative conditioning regimen, indicate the route of administration by choosing at least one of the answer options:

- oral;
- IV (intravenous).

Drug monitoring performed

If the patient received busulfan as part of the myeloablative conditioning regimen, indicate if drug monitoring was performed. If the answer is **Yes**, report the following sub-question.

Total AUC

Total AUC (area under the curve) by specifying the AUC and selecting the unit that the area under the curve was measured in (mg x hr/L, micromol x min/L, mg x min/mL).

Cyclophosphamide

Indicate if the patient received cyclophosphamide as myeloablative conditioning regimen. If the answer is **Yes**, report the **total dose** in milligrams per kilogram or in milligrams per square metre.

Fludarabine

Indicate if the patient received fludarabine as myeloablative conditioning regimen. If the answer is **Yes**, report the **total dose** in milligrams per kilogram or in milligrams per square metre.

Melphalan

Indicate if the patient received melphalan as myeloablative conditioning regimen. If the answer is **Yes**, report the **total dose** in milligrams per kilogram or in milligrams per square metre.

Thiotepa

Indicate if the patient received thiotepa as myeloablative conditioning regimen. If the answer is **Yes**, report the **total dose** in milligrams per kilogram or in milligrams per square metre.

Treosulfan

Indicate if the patient received treosulfan as myeloablative conditioning regimen. If the answer is **Yes**, report the **total dose** in milligrams per kilogram or in milligrams per square metre.

Other; specify

Indicate if the patient received other (other than busulfan, cyclophosphamide, fludarabine, melphalan, thiotepa, treosulfan) as myeloablative conditioning regimen. If the answer is **Yes**, specify the name of the drug in the text field and report the **total dose** in milligrams per kilogram or in milligrams per square metre.

Please consult the LIST OF CHEMOTHERAPY DRUGS/AGENTS AND REGIMENS on the EBMT website for drugs/regimen names.

Gene Therapy Infusion(s) - Description

Complete the Gene Therapy Infusion(s) Description section (questions ''Date of gene therapy infusion'' - ''Reasons for using the back-up product'') for each gene therapy infusion that was performed. There may be multiple infusions of the gene therapy product. Complete this section for each gene therapy infusions by clicking on "+ Add Gene therapy Infusion(s) - Description".

Date of gene therapy infusion

Report the date of the gene therapy infusion.

Did the patient receive concomitant therapy?

Concomitant therapy is given to enhance the function of gene therapy. In cases where a recipient has both HCT and gene therapy, this question applies to the gene therapy infusion, not the HCT. Answer **Yes** if the patient received concomitant therapies in addition to the reported gene therapy, and specify the drugs in the text field.

Answer **No** if there was no concomitant therapy given besides this gene therapy.

Treatment given

If answered **Yes** to the previous question, indicate if concomitant therapy was given:

- **Simultaneously to the gene therapy**

- **After the gene therapy was finished**.

If more than one unit was used, indicate the identification of the gene therapy infusion unit given by the centre as described in the 'Gene Therapy Infusion Unit' section

If more than one infusion unit was used, it is mandatory to indicate the identification of the gene therapy infusion unit given by the centre. If there is only one gene therapy infusion unit with no assigned identification number, enter '1'.

Is the exact number of cells infused available?

Indicate if the exact number of infused cells is available by answering **Yes** or **No**. If the answer is **Yes**, specify details in the subsequent questions.

Number of cells

If the exact number of infused cells is available, specify the number of cells. Enter the value that is not adjusted for cell viability.

Unit (check only one)

If the number of cells infused is available, specify the units for the number of cells by selecting one of the answer options:

- 10^6/kg;
- 10^6;
- 10^8/kg;
- 10^8.

Cell type

Select the cell type for which the number of cells is reported by choosing one of the following answer options:

- **CD34;**
- **T-cells (other than CAR-T cells);**
- **Other; specify** (specify it in the text field).

Cell viability

Report the percentage of cell viability for the corresponding administered gene therapy infusion unit or select **Unknown** if this information is not known.

Was the back-up product infused?

Answer **Yes** if the back-up product was infused.

Reasons for using the back-up product:

Specify the reason for using back-up product by choosing the applicable answer options below (select more than one):

- **Compromise of the gene therapy product after initiation of conditioning and before infusion;**
- **Primary engraftment failure;**
- **Loss of engraftment after infusion;**
- **Other; specify** (specify it in the text field).