

EBMT

European Society for Blood and Marrow Transplantation

CELL THERAPY FORM MANUAL

***A Guide to the completion of the EBMT
Cell Therapy Med-A Form***



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INTRODUCTION

The present document contains information on how to complete the Cell Therapy MED-A data collection form.

It is preceded by the definition of Cell therapy and information on when a new registration should be submitted to the EBMT. For general information on how to register data please visit <https://www.ebmt.org/registry/how-use-registry>

For downloads of the Cell therapy MED-A form and manual please go to <https://www.ebmt.org/sites/default/files/2018-12/25%20Cellular%20Therapy%20MED-A.pdf>

For information on submitting data directly to the EBMT Registry using ProMISe software please refer to: <https://www.ebmt.org/registry/data-submission>

Updated manuals are available to download from the above link. We are grateful for any feedback as to its content (clarity of the definitions, omissions, insufficient background or excessive verbosity, etc.). Please send all comments to the EBMT Registry Office at registryhelpdesk@ebmt.org

CELL THERAPY REGISTRY

The Cell Therapy Registry (CTR) aims to collect data on stem cells, progenitors or mature cells, such as T-lymphocytes, unmanipulated, such as DLI, or sorted and/or cultured and/or genetically manipulated, such as CAR-T cells, and including advanced therapeutic medicinal products (ATMP), used for treatment other than hematopoietic stem cell transplantation (HSCT) as well as data on the clinical characteristics and outcome of the treated patients.

The cells can be infused in combination with other treatments, including hematopoietic stem cell transplantation, or by themselves.

Background

Novel cell therapies include cell preparations defined by various criteria and may be applicable to patients suffering from autoimmune, neurologic and hematologic disorders, heart disease and so on. The therapeutic potential of, for example, cytotoxic T-cells, tumour vaccines and mesenchymal stem cells (MSCs) is undergoing extensive clinical testing in areas such as cancer, tissue repair of connective tissue disorders, heart repair and immunomodulation in the setting of stem cell transplantation.

Although these therapies may be promising and prove to be of clinical use, clinical trials are often small with a limited follow up. The detection of long-term beneficial effects, as well as late and rare side effects would require a large number of patients followed over many years.

Pharma companies are currently developing medicinal products that are classified as gene therapy medicinal products (subcategory of advanced therapy medicinal products) from a regulatory point of view. Similarly CAR-T Cells are classified as gene therapy medicinal products. In all cases, however, the medicinal product is made of living hematopoietic cell that are genetically engineered in vitro to express the wild-type form of a gene that is mutated in the patient, or a fully artificial molecule such as CAR, allowing for improved recognition of target antigens; thus all these products functionally and clinically qualify as “hematopoietic cellular therapies”, and whenever available will add or substitute to BMT.

The CTR collects data on patients treated with these novel cell therapies, to allow for analyses of their risk and benefits.

Registration of new Cell Therapy treatments

The **Cell Therapy Med-A** consists of a registration form and an annual follow up form. The Registration form should be completed and registered in the EBMT Registry database 6 months post cell therapy or at time of death, whichever occurs first. This form should be completed for a procedure in which a patient is the recipient for:

Stem cells, progenitors or mature cells, such as T-lymphocytes, sorted, cultured and/or genetically manipulated, whether the cells be hematopoietic or non-hematopoietic.

A centre must fill in a Cell Therapy MED-A Registration form only if the cell therapy was actually performed at that centre. The centre should not fill in the Registration form if:

- they have acted only as a referral centre
- are only involved in following the patient after therapy which has been performed elsewhere
- the harvest has been performed at this centre but the re-infusion has been performed elsewhere
- the cells are hematopoietic stem cells and the treatment is an HSCT; in this case submit the [HSCT Med-AB data collection forms](#)

How many Cell Therapy Registration forms should be submitted?

For cell therapy procedures in which there is only one instance of cell infusion, it is clear that only one Cell therapy MED-A form will be filled. However, in most cases, cell therapy consists of sequential infusions. This is reflected in the form itself which allows for any number of infusions to be submitted within one registration form.

This is the recommended number of forms that should be submitted:

Description of the procedure	Number of products	Number of MED-A's	Date of this Cell therapy
Therapy with only one cell infusion	Any	1	Date of infusion
Therapy with cell infusions, distributed across several days, overall lasting less than 6 months and given for the same indications	Any	1	Date of 1 st infusion episode is also the Date of this cell therapy . Dates of subsequent infusions will be recorded in the Cell Infusion Episode section.
Therapy with cell infusions distributed across several days, overall lasting more than 6 months and given for the same indication	Any	n	The dates of 1 st infusion episode within the first 6 months interval is the Date of this cell therapy for the 1 st Med-A submitted. The dates of 1 st infusion episode within the second 6 months interval is the Date of this cell therapy for the 2 nd Med-A submitted. Proceed like this until there are no more cell infusions. The dates of subsequent infusions within each 6 month interval, will be recorded in the Cell Infusion Episode section of the corresponding Med-A.
Therapy with cell infusions distributed across several days, overall lasting less than 6 months but encompassing a serious change of indication within that period, for example, due to a relapse or progression of the treated disease	Any	n	Date of 1 st infusion episode is also the Date of this cell therapy for the first Med-A submitted. A change in indication resets the 6 month period, so the date of the 1 st infusion episode after the change in indication will be the Date of this cell therapy for the second Med-A submitted. Proceed like this until there are no more changes in indication. The dates of subsequent infusions within each indication specific Med-A, will be recorded in the Cell Infusion Episode section of that Med-A.

The number of products does not affect the number of Med-As that need to be completed as it is possible to describe any number of products in a single Med-A.

The Cell Therapy - MED-A Registration and Follow up forms contain the Minimum Essential Data that must be registered with the EBMT. It is divided into a Registration form, a series of Disease classification sheets to accompany the Registration form and an Annual Follow up Form.

Timing

All the information contained in the Cell Therapy Med-A form (**Registration** and at least one relevant **Disease classification sheet** if applicable) must be recorded in the EBMT Registry database as soon as possible after 6 months have elapsed since the initial cell infusion for that period or after the patient dies, should this happen before 6 months post cell infusion. No items can be left blank unless specifically stated in the definition. If the item is marked as “unknown”, you will be asked for this information again at the time of data quality checks.

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

Please read below some **possible scenarios** and how to report them using the Cell Therapy form:

Example 1 – a patient has had a previous HSCT and while filling in an HSCT MedA form it was noted that the patient had cell therapy for the first time 08/02/2016 and then went on to have a second infusion 15/06/2016 for the same reason.

- ➔ It is ok if you first use the HSCT MedA form to record the HSCT, where you can fill in the relevant DLI date and other information. After you finish and save, you can use the Cell Therapy MedA form (by using code 21 in Promise), and use the same infusion date. Please note that it doesn't matter if you have already recorded some of the Cell Therapy information. You can simply tab through the completed items, until you get to any unanswered ones. On page 7 of the form you put **1** for the 'Chronological number of cell therapy treatment for this patient' and then on page 9 you answer 'Yes' to 'Was there more than one cell infusion episode during this treatment/procedure' and replicate the '**Cell Infusion Episode**' section with the relevant dates for each episode. On the first Episode page, you will write "**1 out of 2**" episodes, and in the second Episode page (copy) you will write "**2 out of 2**". The reason you are to use the same Cell Therapy form here, is that it is both within a 6 month period and it is for the same Indication.

Example 2 – A patient has had a previous HSCT and it was noted that the patient had DLI for the first time 08/02/2016 for Relapse and then went on to have a second infusion 15/06/2016 for GvHD.

In this scenario, you would have to use 2 separate forms (pages 1-9, excluding the Diagnosis sheet, if applicable) for each infusion. The reason for this is that you have 2 different Indications: 1st for **Primary Disease treatment**, which is the Relapse (code 1 in Promise), and then 2nd for GvHD, which is a **Complication of the Disease** (code 2 in Promise). Please note that, although very rare, there can be a case where you would have **one infusion for both Relapse and GvHD**, which is why there is also code 3 in Promise "Both Primary Disease AND Complications".

Example 3 – A patient has had a previous HSCT and then it was noted that the patient had cell therapy for the first time 08/02/2016 and then went on to have a second infusion on 01/10/2016 (for the same reason)

- ➔ In this example, you would use 2 separate MedA Cell Therapy forms. The reason for this is the time interval being **over 6 months**, even though the reason is the same. So, you would complete one registration form for the infusion on 08/02/2016 only, and then complete another registration form for the second infusion, in which, on page 7, you would state that the chronological number is 2 and then on page 9 say 'No' to 'Was there more than one cell infusion episode during this treatment/procedure'.
In terms of time, note that the 6 months period would be reset if the Indication changes.

Example 4 – A patient has had a previous HSCT and it was noted that the patient had cell infusion for the first time on 08/02/2016 for GvHD and then went on to have a second infusion 01/10/16 for Relapse.

- ➔ Again, you would have to use 2 separate forms, because there are 2 different Indications (reasons), namely **GvHD** and **Relapse**, and also the time interval is **over 6 months**.

Cell therapy treatment in the presence of HSCT treatments in the same patient

In many cases, the cell therapy is given to patients who have already received or are about to receive an HSCT. For example:

1. Cell therapy given as part of the transplant treatment immediately before or on the same date as the HSCT date.
 - a. The HSCT should be registered first following the standard MED-AB HSCT forms, and the cell therapy should be registered afterwards using the Med-A Cell therapy form. This is true even in the case in which the cell therapy date is before the HSCT date.
 - b. Do not include the HSCT conditioning drugs when submitting the cell therapy form
2. Cell therapy given after the transplant treatment.
 - a. Register the cell therapy 6 months after the 1st cell therapy infusion date as you would do if there had not been any HSCT.

Follow up

Follow up should be submitted annually, from the date of the 6 month followup. Only one follow up form needs to be submitted per patient regardless of the number of cell therapy infusions they may have received.

NOTE: at the moment the HSCT and Cell Therapy follow up forms are different and separate. It is the intention of the Registry to combine them so that only one follow up episode per year needs to be entered into the database, whether the patient has or has not received also HSCTs. Unfortunately, this is not the case at the moment.

INSTRUCTIONS

IDENTIFICATION

CENTRNR EBMT Centre Identification Code (CIC)

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

<http://www.ebmt.org/Contents/Members-Sponsors/Members/MembershipList/Pages/Membership-List.aspx>

If you are not a member of the EBMT contact the Executive office at membership@ebmt.org
This item is essential for correct registration of your data.

Hospital

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

UNIT Unit

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

MEDNAME Contact person

Write down the name of the person who will be responsible for updating or correcting the data recorded in the EBMT Registry database should this be necessary.

E-mail

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

DAT1STRE Date of this report

If you enter the data directly from the patient notes, it is the date you are entering the data. If you fill in a paper Med-A form, it is the date you filled in the form, not the date when you recorded it in the database. This date will remain unchanged regardless of how much more data you add to the patient record.

Unique Identification Code (UIC)

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

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

IMPORTANT NOTE: All data for a patient should be entered under the same UIC number
This includes subsequent transplants and Cell Therapies.

Patients transferred to other centres for further treatment must always keep their original UIC number. If your patient had a prior treatment elsewhere please use the form **Data access request** form found in the link below to request access to their existing UIC:

[Patient Given Previous Treatment in Other Centre.pdf](#)

UPN Hospital unique patient number or code

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

GIVNAME Initials (first name(s) - surname(s))

FAMNAME Write the initial of the first name of the patient followed by the initial of the surname of the patient. In countries where it is customary to do so, you can write down the initials of the first and second surname of the patient after the initial of the first name. If the local hospital guidelines or national law do not allow initials to be provided to third parties, you can write a code which has the approval of your hospital. Make sure there is consistency in the way the identification of the patient is given so the record can always be traced even if the patient remains anonymous.

DATPATBD Date of birth

Write the date of birth of the patient. If you do not know the exact date, apply the following: If you know the month and year but not the day, use "01" as day; If you do not know the month, use "01" (January) as month. Indicate that the date is approximate if applicable.

PATSEX Sex

Indicate the gender of the patient.

INDICATION FOR TREATMENT

INDICAT Main indication

Select the indications for the cell therapy treatment. The treatment may be aimed at more than one indication.

DISMCLFD Treatment of a Primary disease including Infections or Infection prevention

This means that the treatment of a primary diagnosis or disorder is the reason for cell therapy, i.e. heart disease (angina pectoris, heart failure), multiple sclerosis, inflammatory bowel disease, haematologic malignancies (acute leukaemia).

In the case of infections, not only the treatment of the infection but its prevention is also considered here.

- Tick a box for the disease for which the patient is being treated and then complete the relevant disease classification sheet (please see below section 'If indication is Primary disease').
- Note that Infection is one of the primary diseases listed.
- Do not tick boxes for diseases the patient may have had in the past if the procedure being reported is not meant to deal with them.

Treatment or prevention of complications derived from a previous transplant (HSCT)

This means treatment (such as mesenchymal cell infusion) that is used to treat a complication associated to a previous hematopoietic stem cell transplantation (HSCT), i.e. graft-versus-host disease, graft failure etc.

Both

It is possible to have cell therapy infusions for more than one indications

Other indication is an option of last resort and generally should not be used. If you find yourself in a position where this is the best option, please contact the Registry helpdesk before proceeding at registryhelpdesk@ebmt.org

If indication is Primary disease

IDAABB

Date of diagnosis

As the patient is being treated for a primary disease write down the date of diagnosis of the disease for which the patient is being treated.

Infections as indication

If there is an infection and the treatment is aimed at treating it, the date of diagnosis is the date the infection was detected.

If there is no infection and the treatment is aimed at preventing the occurrence of an infection (prevention of CMV reactivation, for example), use the date of the HSCT (or other treatment) that is feared could lead to the infection.

After selecting the main indication, find the correct **Disease specific sheet** corresponding to that main indication.

In each **Disease classification sheet** you will find the sub-classification and the disease status, if applicable, for each diagnosis. Please, use the [Med-AB Forms Manual](#) for information on how to fill these pages.

Infection as indication**Prevention/prophylaxis or Treatment**

Cell therapies can be given either to prevent an infection usually in the context of an HSCT or to treat an infection that has already taken place.

In both cases, please indicate the pathogens involved

Pathogen involved

Indicate the organism for which the patient is receiving a cellular therapy. Select the pathogen corresponding to the identified infection as reported on the microbiology, laboratory report, or other physician documentation. If the specific organism is not listed, use the “other, specify” and report the name of the organism in the space provided.

If indication is related to Haematopoietic stem cell transplant (HSCT)

If this cell therapy is in relation to a previous stem cell treatment, this original treatment must be registered first. Therefore, please search the registered HSCTs for this patient. If the patient is already registered, ensure the data for the HSCT is also registered before adding this cell therapy treatment to that record. If the patient and/or the relevant HSCT of that patient are not registered, you must first register the patient and the relevant HSCT Med-A form before adding the cell therapy form.

If the patient had the HSCT in a different institution, you will not be able to search for it. In this case, you must contact the Registry helpdesk before registering the patient to be given access to the patient’s existing record.

IDAABC

Date of first cell infusion

Date of the first cell therapy infusion of the treatment. For patients receiving cell therapy for a complication of HSCT, put date of first cell therapy treatment, not date of HSCT.

CELL THERAPY TREATMENT

CTCLNSETTN

Clinical setting: (tick only 1 box)

Clinical trial: - Tick this box if the patient is enrolled in a clinical trial.

Phase - Indicate the phase of the trial

Blind trial - Indicate if this is a blind trial. That is, a trial where the treating doctor does not know which of the treatments offered in the trial is being given

Randomised trial – Indicate if the treatment is allocated randomly to the trial subjects

Eudract no - this is the number given to the trial when registered with the European Clinical Trials Database

USA CT number – if the trial also runs in the USA, there should also be a USA clinical trials number

UMIN CT number - if the trial also runs in Japan, there should also be a Japanese clinical trials number

Indicate if you want this registration hidden

If the patient is included in a clinical trial, it may be necessary to hide the data from other researchers until the results have been analysed and published. If this is the case, answer **Yes** here and indicate the approximate date until which the data must be hidden. Should the trial end before or after expected, this date can be changed in the future.

Institutional guidelines / standard treatment - Tick this box if the patient is treated with cell therapy according to the treating centre's policy

Hospital exemption - Tick this box if the patient is treated with cell therapy under Hospital exemption. It is a regulatory framework under which some cellular products can be administered to patients outside clinical trials, even if the products are not yet registered.

Compassionate use - Tick this box if the patient is treated under Compassionate use. It is a regulatory framework under which a cellular product can be administered to a specific patient outside a clinical trial, for medical reasons, upon request and approval from regulatory agencies.

PERFSYST
KARNOFSK

Performance score

The **Karnofsky and Lansky** are standard performance scales, which can be found in [Appendix I](#) of this manual. The Karnofsky is used for adults and the Lansky is used in paediatrics.

The **ECOG** (Eastern Cooperative Oncology Group) Performance status, briefly known as ECOG, is also frequently used. It has 5 levels against the 10 of the Karnofsky and Lansky. See [Appendix I](#)

CETHORIG

Cell origin:

Indicate whether the cells infused proceeded from the patient or from another person.

Autologous the patient receives his/her own cells back

Allogeneic the patient receives a cellular therapy product prepared from cells harvested from another person

Product manufactured from

- a new donor –related or from a Donor registry- which has not been registered before but for which you have data.
- a donor that has been used before either for previous cell therapy or for a previous HSCT, and that has already been registered. If that is the case, you can select this option and there is no need to fill in the **Donor** section again.
- an unknown donor for whom there is no data. This may happen in some commercially manufactured products. If you select this option, the questions on the donor section can be skipped.

DONRL

DONOR**HLA match type**

Differences in histocompatibility (or degree of match) affect the outcome of cell infusions. We define histocompatibility by looking at differences in certain proteins (or antigens) between the patient and their donor (also called “tissue typing”). The antigens which are most important in the matching procedure are the major HLA-antigens. The genes encoding these antigens are found on chromosome 6. Each individual has two copies of chromosome 6, each copy inherited from one of the parents.

Related donors

If the patient and their donor have the same parents and the HLA antigens are identical, it is most likely that both siblings have inherited the same copies of chromosome 6 from each parent and are therefore ‘genotypically’ identical, i.e. both siblings have the same genes for the HLA antigens. This is an **HLA-identical sibling** donor.

Twins develop from a single egg (monozygotic) or two eggs (dizygotic). If the donor is a monozygotic twin, known as “identical twins” the donor is defined as **syngeneic** and the histocompatibility genes in donor and patient are the same. However, if the donor is a dizygotic twin, the histocompatibility should be defined as for any other sibling transplants.

Occasionally other family members (parents, cousins, half siblings etc) could also be HLA-identical to the patient but could not have inherited the same copies of chromosome 6 as the patient (because they don't share the same parents). This is defined as an **HLA-matched other relative**.

The donor can also be a family member (sibling, etc.) but with different HLA antigens. That would be an **HLA-mismatched related**.

HLA locus mismatch.

The degree of mismatch indicates how many loci have at least one mismatch. It is used as an approximation to the identification of haplotypes.

Unrelated donors

When the donor has no family connection to the recipient it is called **unrelated donor**. These donors are found through an unrelated donor registry and information on the donor registry is requested.

ION (Issuing Organisation Number)

Most existing donor registries are being given an issuing organisation number known as ION, by the WMDA. The number can be found in ProMISe and the WMDA list is available on:

<https://share.wmda.info/display/WMDAREG/Database>

This list also contains some, but not all, the Cord Blood banks. Please enter this number in the form. For reference you can find a [conversion table](#) of the ION codes and the former BMDW codes on our [Helpdesk web page](#).

Name

Please, enter the name of the donor registry, or, in case of cord blood, the name of the cord blood bank, and if applicable, Donor centre name in full. This is particularly important if you do not know the Donor Registry code.

Identification of the donor

It has become increasingly important from the clinical and the legal point of view, to be able to use joint information for the patient and donor(s) pair for each treatment. For this reason, it is important that, while keeping anonymity, the donor data can be traced. This can only be done if the unique identification codes for the donors are stored.

It is for this reason that the EBMT is requesting the donor code given by the centre, the donor registry and/or the cord blood bank together with the patient id these institutions give to the recipient.

Date of Birth and Sex of Donor

DATDONBD

Please fill in the date of birth of the donor (or his/her age) and their gender.

CELL THERAPY INFUSION UNIT (CTIU)

For the purposes of this manual, a single Cell Therapy Infusion Unit is defined as:

1. Cells collected from a single donor using the same collection method regardless of the number of collection days, and manipulated in the same way.

OR

2. Different cells being manipulated or modified by different methods but combined into one bag at the end of the manufacturing process and delivered as a single treatment. This can be particularly true for commercially available products, manufactured outside of the premises.

If cells are collected from the same donor but are manipulated in different ways and administered from different bags, they would be considered different infusion units.

If cells are collected from different donors and administered from different bags, they would be considered different infusion units.

Any bag that has its own batch number will be considered a separate infusion unit.

More than one cell infusion unit administered?

If according to the above definition, more than one unit is to be infused, you should answer “Yes” here. In that case, the Cell Therapy Infusion Unit – Description and collection section should be replicated and filled in for each cell infusion unit.

Example: if CART cells are produced from the same collected cells, manipulated with the same protocol, but are then separated, and stocked in different bags, with different batch numbers, they are two different cell infusion units.

Identification**Name of the manufacturing facility**

Report the name of the facility which manufactured the CTIU (pharmaceutical or biotech company, cell processing laboratory or another site)

Name of the package

Report the package name.

Batch number

Report the Batch number of the CTIU, if applicable.

Identification of the Cell Infusion Unit given by the Centre

Report the CTIU identification given by your centre. This information is **mandatory** if more than once cell infusion unit has been used in the same treatment.

CIUBMRRW Tissue source

Tissue from which the cells were collected, for example, bone marrow, adipose tissue, muscle. You can tick more than one.

Cell types

Select all cell types of the cellular product that are collected for this CTIU. You can tick more than one. If the cell type is selected as ‘Other’, specify the other cell type.

CIUBSAMTHD Collection procedure

Although, the collection method may depend on the tissue from where the cells are collected and also the type of cells collected, in some cases different collection methods can be used for the same end result. For this reason, it is important to know which method was used.

It is possible that more than one collection procedure has been used for one infusion unit when the latter is sold as a unique commercial product.

CIUCOLLDAT Date of the 1st collection

The donation procedure starts with the first injection of a mobilising agent, the start of anesthesia or the start of apheresis (in case of non-stimulated leukapheresis, e.g. for DLI/NK or any other therapeutic cells)

For example:

-**Bone marrow**: the date of bone marrow collection (date of procedure is the same as the first date of collection)

-**Non-stimulated leukapheresis**: day of the (non-stimulated) apheresis

Number of collections

Indicate on how many occasions were cells collected from the donor or patient. You should only include those collections whose product was used for this particular CTIU.

CIUMOBAGNT Mobilising/modification agent used

Growth factors (cytokines) are given for the collection of stem cells from the peripheral blood. They can also be used prior to the collection of bone marrow but this is less common. List name(s) of the drug(s) (chemo, growth factors, antibodies, etc.) used for mobilisation/activation/modification of the cells that were being collected.

Drugs used for mobilisation should only be answered positively if the drugs are used for actually mobilising the cells: pain killers, etc. should not be reported here.

CTIU MANIPULATION

CIEXVIMANI Ex vivo manipulation

Refers to treatment of the collected cells in the laboratory before infusion into the patient.

Indicate if the cells contained in the CTIU were selected (i.e. selective retention of a population of desired cells through recognition of specified characteristics), modified or genetically engineered.

Manipulation laboratory

Indicate where the manipulation took place.

Drugs

Mitogens - The cellular product was prepared by exposing the cells *ex vivo* to a compound that promote their activation and proliferation

MANIDRGGF Growth factor - The cellular product was prepared by exposing the cells *ex vivo* to a growth factor

Other type - The cellular product was prepared by exposing the cells *ex vivo* to another type of drug

MANIGENE Gene manipulation

Gene transfer

This is a procedure by which techniques of gene transfer/transduction are used to alter the structure and characteristics of genes in the graft before the cell infusion. This is an experimental procedure which is used in cases of inborn errors or cancer, but some products have been recently approved in Europe, and we may expect their extended use in the near future.

Retroviral vector – These vectors are used to genetically modify the cells. Add name of the used vector
Retroviruses are any group of RNA viruses that insert a DNA copy of their genome into the host cell to replicate. HIV is an example of a Retrovirus

Lentiviral vector - These vectors are used to genetically modify the cells. Add name of the used vector.
Lentiviruses are members of the genus of retroviruses that have long incubation periods and cause chronic, progressive, usually fatal disease in humans and other animals.

Other - specify the type of vector used. Non integrating vectors, including RNA electroporation, should be listed here.

N. of gene transfer cycles - Genetic manipulation can be performed by exposing cells to the vector once or more than once, to increase the efficiency of the procedure. List here the number of gene transfer cycles that were used to manufacture the cellular product infused to the patient.

Transgene - Transgenes are the genes that are introduced in the vector, and through the vector to the cells, to manufacture the cellular products.

Indicate the transgene used.

- | | |
|--------------|--|
| CAR | - specify the target recognized by the CAR |
| Suicide gene | - specify the name of the suicide gene |
| TCR | - specify the target recognized by the TCR and the HLA restriction element |
| Other | - specify the type and name of the transgene |

Gene editing

Indicate if the cells underwent a type of genetic engineering in which DNA is inserted or removed from a genome using artificially engineered nucleases. Artificially engineered nucleases include Zinc Finger Nucleases (ZFN), TALEN and CRISPR/Cas9. Specify the gene manipulated.

Other Gene manipulation

Indicate if a different genetic manipulation not previously listed was used.

Recognition of a specific target / antigen.

In some cases the cellular products are specific for a target: ie: CART cells (specific for CD19, or other molecules) or viral specific T cells. If this is the case, please specify the target.

Selection

CTIUSELECT

Positive

Selection of cells for example by the monoclonal antibody that select only certain types of lymphocytes. The selected cells are used for the cell therapy.

Negative

Cells are destroyed (or removed) from the product, either with some drug like cyclophosphamide derivatives, or with specific antibodies that bind to them.

Purity: This is the percentage of the selected cells among the total number of cells in the final product. For example, if T cells are to be infused and after the manipulation the end cellular product is composed of 99% T cells and 1% NK cells, purity will be 99%.

Yield: This is the percentage of selected cells in the final product against the total number of those same cells in the pre- manipulated product. For example, if the unmanipulated product contained 50 T cells, and after the selection process, only 40 T cells are left, the yield is $40/50 \times 100 = 80\%$

CTIUEXPNS

Expansion

This is a procedure meant to increase the number of collected cells in the laboratory before infusion, and can require a variable number of days. For some cellular products, such as mesenchymal stem cells, the number of passages (ie. times in which the cells are diluted) is more useful than the n. of days in culture to estimate in vitro expansion. Therefore, depending on the type of cellular product used, number of days in culture or N. of passages could be ticked and specified.

Expansion fold - Please add the ratio of cells at the end of the manipulation procedure /cells at the beginning of the manipulation procedure.

Ie: if you start the culture of 50 lymphocytes, and after 10 days you have 500 lymphocytes ready to be infused. The expansion fold is $500/50 = 10$ fold.

Induced differentiation

Some cellular products are differentiated cells obtained in the laboratory by culturing cellular precursors in specific culture conditions. For example, if the cellular product is “dendritic cells”, it can be obtained by culturing monocytes harvested by leukapheresis, and cultured in the laboratory with cytokines and growth factors that induce their differentiation into dendritic cells.

Freezing

Answer ‘yes’ if the cellular product has been frozen and thawed before infusion at any time point between collection and infusion.

TREATMENT

CELLTHNR

Chronological number of cell therapy for this patient

Refers to cycles of cell therapy, when applicable, in which the 1st infusion is given more than 6 months apart or when the indication for the cell therapy has changed. If patients receive several infusions within 6 months for the same indication, this is stated under CELL INFUSIONS EPISODES and not here.

If this is not the first Cell Therapy treatment for this patient, please indicate:

- if the same Cell Therapy Infusion Unit is being used as for the previous treatment.
- the date and type of the previous treatment.
- If allograft, indicate if the same donor has been used for all previous and current cell therapy.
- If the patient has received a treatment in another institution, please indicate the centre’s CIC if known. If not known, write down the name of the institution and its city.

REASPRMCT

Reason for the treatment

If the patient is treated for the primary disease, indicate the main reason.

VEASDL1

If the patient is treated for a complication related to a previous treatments, answer the questions related to GvHD, graft function and immune reconstitution. and the indication: is it meant to prevent the occurrence of the complication (prevention) or is it meant to treat it?

VCONDITI Patient preparative treatment

Indicate whether the patient is treated with chemotherapy or other drugs in the context of the cell therapy infusion. If so, indicate the drugs and doses used here.

In the event of the cell therapy infusion unit being infused at the same time as an HSCT taking place, the HSCT conditioning/preparative treatment is not to be reported here. In these cases, the correct answer to the question Patient preparative treatment would be “No”.

The same drug may have several different names depending on the country or product. If you cannot find the drug in the drop down menu, before deciding that the drug is not listed, consult the existing drug list (**LIST OF DRUG NAMES & SYNONYMS**) which you can find in the EBMT website:

<http://www.ebmt.org/Contents/Data-Management/Registrystructure/MED-ABdatacollectionforms/Documents/MEDAB0084.pdf>

This document provides alternative names for many of the drugs.

Only use Other when you are absolutely sure the drug is not listed. In this last case, write the name of the drug in full and clearly; do not use abbreviations.

Indicate the prescribed dose and the units in which the dose is given for each agent. Do not provide daily or weekly doses, but the **final cumulative** dose received by the time the regimen has ended. For example, if the dose of a particular drug is 100 mg/m² on days 1 and 2, then 100 mg/m² x 2 days=200 mg/m² and the dose to be entered should be **200 mg/m²**.

The units listed are those most commonly used. If the units used in your centre are different, please try to convert the dose as necessary to one of the listed units. If this is not possible, write on the margin the name of the units used.

VOTHERT Other type of treatment

Indicate here if any additional treatment was given. I.e: radiotherapy, photopheresis or any other medical procedure.

CELL INFUSION EPISODE

For the purpose of this manual, a cell infusion episode is the infusion at one point in time of one or more cell infusion units (CIU).

If two different CIUs are infused simultaneously or within a short interval (hours rather than days), that will be considered **one cell infusion episode**.

Alternatively, if the same CIU is infused on two different days, that would be considered **two cell infusion episodes**.

Indicate whether there are more than one cell infusion episode during this treatment. For each cell infusion episode, indicate the date of the cell infusion episode

TISSUERT ARTERRT etc Route of infusion

Indicate in which way were the cells administered.

Systemic including Intravenous

Intravenous infusion into the veins – examples include infusion via central line or via catheter.

Local, specify the different local routes

Intra-arterial	infusion within an artery or arteries.
Into tissue	infusion in a restricted area of the body or in a tumor that cannot be classified as organ; it also includes implantation of cells on matrix (i.e. cells allowed to adhere to an implant device, such as collagens, sponge, in the laboratory, where one or several such sponges are plated in the patient).
Intraperitoneal	infusion within the peritoneal cavity.
Intrathecal	infusion within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles.
Intramuscular	infusion within a muscle.

Intrabone	Also known as Intramedullar - infusion into the marrow cavity within a bone, such as directly into the left or right iliac crest.
Intraorgan	infusion within an organ such as the heart, liver, lungs, etc.

If the route of infusion is not one of the above options, select “Other route” and specify the infusion route.

MONNCEL
MESECHYM

Cells infused

Indicate the composition of cells used for the therapy. For example, whole bone marrow encompassing several types of cells, mononuclear cells derived from bone marrow, mesenchymal stem cells etc. One or several types of cells might be used to treat the patient during the same cell infusion episode.

In the case of target specific lymphocytes, please specify the target:

Pathogen specific - Specify the pathogen targeted by the cell based cellular product

Tumour specific - Specify the antigen targeted by the cell based cellular product

Number of cells – For each type of cell, indicate the cumulative number of cells received by the patient in the cell infusion episode.

PROCED

Other type of treatment

Depending on the disease, the patient may receive other type of treatment together with the cell therapy, for example, they may receive the cells at time of coronary by-pass surgery, spinal cord decompression, etc. It is important to know whether this was the case or whether the patient was not undergoing such concurrent treatment. Do not include here the preparative regimen, if any.

When was this other type of treatment given

Indicate when was this type of treatment given in relation to the cell therapy infusion episode: Simultaneously to the cell therapy infusion / After the cell therapy episode was finished.

TUMRSA2

RESPONSE

LABSTAT

Given the different types of indications, the response parameters will vary greatly. It can include clinical, biological and/or laboratory responses. Give the best response obtained in the timeframe analysed (ie first 6 months for the first form, or the following 12 months for the Annual follow up form)

See [Med-AB Manual for HSCT](#) for the definition of response in most primary diagnosis.

DATRESP

Date response measured - Indicate the date in which the best response was assessed.

Examples would include disappearance of all symptoms of graft-versus-host disease in patients treated with MSC for this disorder; improvement of heart failure in patients treated with cell therapies after myocardial infarction; or reduced inflammatory lab parameters in patients with rheumatologic disorders; etc

If the treatment has been given for a primary disease and also for a complication, the response to each of them must be given separately.

NOTE: From here onwards the manual covers both the 6 month assessment and the annual follow up

SIX MONTH ASSESSMENT OR ANNUAL FOLLOW UP

IDAABE

After entering all the cell infusion episodes that constitute this treatment, you should provide the status of the patient at 6 months after the 1st cell infusion episode of the treatment.

If patient died before the 6 months had elapsed, enter the date of death, otherwise enter the date the patient was seen as close as possible to the date of the 1st infusion episode in this cell therapy treatment + 6 MONTHS.

If the patient cannot be traced (for example, left the country), put the exact date the patient was last known to be alive under assessment date or death and tick the box ‘lost to follow up’ in the Survival Status section at the bottom of the form.

TOXICITY DURING THIS PERIOD

AGVHGRMX

Acute Graft Versus Host Disease

Acute graft versus host disease (aGvHD) is a consequence of donor T-cells recognizing the patient's antigens as foreign. It usually consists of dermatitis, hepatitis and gastroenteritis. Although it tends to appear within the first 100 days, it can also appear later on.

Time is no longer used to determine the type of graft versus host disease, and the NIH (National Institute of Health) consensus recognises the following possibilities

NIH consensus

- 1) acute GvHD (absence of features consistent with chronic GvHD), comprising:
 - classic acute GvHD (before day 100), and,
 - persistent, recurrent, or late acute GvHD (after day 100, often upon withdrawal of immunosuppression);
- 2) chronic GvHD , comprising:
 - classic chronic GvHD (no signs of acute GvHD), and,
- 3) overlap syndrome, in which features of both acute and chronic GvHD are present.

aGvHD Manifestation

DATAGHV

Date of onset is important.

Maximum grade, grade I, II, III or IV

The maximum grade for acute graft versus host disease (aGvHD) is defined according to the stage presented by the skin, liver and gut. Up until 2015, there was only one stage for gut which included the symptomatology of diarrhoea, nausea and vomiting. Currently, Gut is being subdivided into Upper gut and Lower gut as shown in the following staging table:

Organ	Stage	
Skin	0	No rash attributable to acute GVHD
	1	Skin rash < 25% body surface
	2	Skin rash 25-50% body surface
	3	Skin rash >50% body surface erythroderma
	4	Generalized erythroderma with bullous formation, often with desquamation
Liver	0	Bilirubin < 34 micromol/L
	1	Bilirubin 34-50 micromol/L
	2	Bilirubin 51-102 micromol/L
	3	Bilirubin 103-255 micromol/L
	4	Bilirubin > 255 micromol/L
Lower Gut	0	No diarrhoea attributable to acute GVHD / diarrhea \leq 500 mL/day
	1	Diarrhoea volume 501 - 1000 ml/day
	2	Diarrhoea volume 1001 - 1500 ml/day
	3	Diarrhoea volume \geq 1501 ml/day
	4	Severe pain with or w/o ileus
Upper Gut	0	No persistent nausea or vomiting
	1	Persistent nausea or vomiting

The maximum grade seen during the relevant period being studied is calculated from the table below.

grade 1: Skin stage 1 or 2	AND	Liver stage 0	AND	Upper Gut stage 0	AND	Lower Gut stage 0
grade 2: Skin stage 3	OR	Liver stage 1	OR	Upper Gut stage 1	OR	Lower Gut stage 1
grade 3:		Liver stage 2 or 3	OR			Lower Gut stage > 1
grade 4: Skin stage 4	OR	Liver stage 4				

The overall grade (or the stage of skin, liver and or gut) should be mentioned in the patients' file. If not clearly stated, ask your physician.

Related to Cell Therapy

Please state if the aGvHD was related to the current Cell Therapy treatment.

VGVDRES aGvHD resolved?

Indicate if the aGvHD was resolved completely before the 6 month assessment date, or the last follow up date according to the form being completed.

Chronic Graft versus Host Disease (cGvHD)**GRAVHOSD Onset of cGvHD**

Mark; “No (*never*)” if the patient has never yet had an episode of cGvHD.

If the patient has had an episode of cGvHD, mark “Yes” and then indicate the date of onset of cGvHD for this episode.

Maximum extend

Please mark the grade, ‘limited’ or ‘extensive; this information should be in the patient’s file or ask your physician. cGvHD is considered limited if it is present only in the liver and/or a localised area of the skin. If the cGvHD affects any other organ(s) or there is generalised skin involvement, it is considered to be extensive. Tick only one box.

Maximum NIH consensus score

The NIH scoring system was first published in 2005 and has since been validated several times. As described in [http://www.bbmt.org/article/S1083-8791\(14\)01378-0/pdf](http://www.bbmt.org/article/S1083-8791(14)01378-0/pdf), eight organs or sites (skin, mouth, eyes, gastrointestinal tract, liver, lungs, joint and fascia, and genital tract) are considered for calculating global score. Elements included in the proposed global scoring include both the number of organs or sites involved and the severity score within each affected organ.

The scoring is complex and needs to be recorded by the physician. The quoted publication contains an extensive description of the necessary measurements to obtain the score. Indicate the maximum NIH score during this period, as per the results of these measurements.

Other Complications or toxicities during this period

Some toxicities have been already reported and associated to some cellular therapy approach (IE cytokine storm has been observed after infusion of CAR T cells). However, since cellular therapy is still highly experimental, any kind of toxicity should be carefully monitored and reported to gain information on each cellular product and protocol.

IDAABECA Cytokine storm

Cytokine-associated toxicity, also known as cytokine release syndrome (CRS), is a non-antigen specific toxicity that occurs as a result of high-level immune activation.

CRS revised grading system (Blood First Edition paper, May 29, 2014; DOI 10.1182/blood-2014-05-552729):

Grade 1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
Grade 2	Symptoms require and respond to moderate intervention Oxygen requirement >40% or Hypotension responsive to fluids or low dose ² of one vasopressor or organ toxicity
Grade 3	Symptoms require and respond to aggressive intervention Oxygen requirement >40% or Hypotension requiring high dose* or multiple vasopressors or organ toxicity or grade 4 transaminitis
Grade 4	Life-threatening symptoms Requirement for ventilator support or organ toxicity (excluding transaminitis)
Grade 5	Death

Neurotoxicity

Neurotoxicity is the development of different neurologic signs and symptoms reported after the infusion of genetically modified lymphocytes. This was initially thought to be part of CRS, but it was also observed in the absence of any other signs of CRS. Neurotoxicity also appears to be a spectrum of signs and symptoms that vary from fine tremors and word finding difficulties to seizure and loss of conscience. This section collects different neurologic signs that have been described after cellular therapy infusions.

Indicate if neurotoxicity occurred and report the date when the first symptom of neurotoxicity was documented by a physician or other health care provider in the progress note or chart.

Neurotoxicity description

Visual hallucinations: The sensation of seeing objects that are not really there.

Altered mental status: It is a disruption in how the brain works that causes a change in behavior. This can happen suddenly or over days and ranges from slight confusion to total disorientation and increased sleepiness to coma.

Tremors: Tremor is caused by the rapid alternating contraction and relaxation of muscles (involuntary) and is a common symptom of diseases of the nervous system.

Aphasia: The loss of ability to understand or express speech, caused by brain damage.

Hemiparesis: Paralysis of one side of the body.

Seizure(s): Uncontrolled electrical activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbances or a combination of symptoms.

Grade IV Organ toxicity (Liver, Lungs, Heart, Kidney, Other, specify)

Bone marrow aplasia/failure

Other complications

Related to Cell Therapy

Please state if the complication was related to the current Cell Therapy treatment.

Ongoing

Tick if there was no resolution and the reported complication episode is still present at the 6 month assessment.

Date of resolution of the complication

The day that the medication or other treatment was stopped is NOT necessarily the resolution date. Resolution should be determined after clinical investigation and will be mentioned in the patient's file.

SECONDARY MALIGNANCY

Patients can develop secondary disorders. If this is the case, tick "Yes", provide date of diagnosis and indicate which diagnosis. This can be any malignant disease for which the patient had not been diagnosed before the transplant.

Indicate if the malignancy appears in the cellular product.

GRAFT ASSESSMENT

This question should be answered only for patients who have previously received a transplant.

Graft loss happens if neutrophils increase to $\geq 0.5 \times 10^9/L$ for at least three consecutive values and subsequently decrease to a low level until additional treatment to obtain engraftment is given. Note that sometimes neutrophils can temporarily decrease to $< 0.5 \times 10^9/L$ (due to viral infections, medication or GvHD) and can return to $\geq 0.5 \times 10^9/L$ on recovery.

In allografts, there can be graft loss with normal blood levels due to autologous reconstitution. A chimaerism test (see Haemopoietic Chimaerism below) can determine whether or not there has been a graft loss. If the test has not been done, please answer "not evaluated".

LAST DISEASE AND PATIENT STATUS

First Relapse or Progression or Significant worsening of organ function

Only answer this question if one of the indications for the cell therapy is the primary disease.

Relapse means the occurrence of new sites of disease, or the re-occurrence of disease or systemic symptoms (B symptoms) after having achieved a complete remission which lasted for 3 months or more. It is called *progression* if CR lasted less than 3 months. Progression also describes any worsening of the disease status in patients previously assessed as not in CR.

1st relapse: means the first relapse that occurs after a first CR has been achieved.

If CR was never achieved, you can skip this question, but make sure you marked "No" under "CR achieved" above.

If CR was achieved and there was no 1st relapse, mark "No".

If the patient has never had a CR, the status of the disease cannot be relapse, but it can be progression.

Last disease status

Indicate the status of the primary disease or of the complication the cell therapy was meant to treat or prevent on the date of the 6 month assessment or the last follow up, as applicable.

VPATSTAT**Survival status**

Provide the most recent information you have. The status must be the status at the Date of last contact and the latter must be either the very last date the patient was known to be alive or the date of death if the patient is known to have died.

Main cause of death

The information on cause of death is very important. Tick only one major cause of death. Please check with your physician since this information is sometimes difficult to find in the patient's file.

Relapse or progression

HSCT related

Cell therapy related

In the absence of clinical disease, a death caused by complications or infections after cell therapy is considered treatment related. If the patient has not had any HSCT, the cause of death would be considered Cell therapy related. However, if the patient had also had an HCST, it may also be HSCT related. Check with your physician.

In the presence of clinical disease, if the disease is progressing, the death will be considered as Relapse or progression, even if there are complications or infections during the post cell therapy infusion period. However, if the disease was stable, or there had been an improvement after cell therapy, and the patient were to die of complications or infections, the death would be considered treatment related.

Persistence of the Infused Cells

This section relates to the evaluation of persistence of a cellular product in the recipient. It only applies to cellular products that can be identified either by being genetically disparate (unrelated donor) or if it is genetically modified.

Methods such as PCR assays, flow cytometry (immunophenotyping), imaging, immuno histochemistry or chimerism studies can be used to detect persistence of the cellular product in the recipient. If tests were performed to detect persistence of the cellular product since the date of the last report, select "yes" and enter the date of the test.

Indicate whether tests were performed to detect the persistence of the cellular products and the method used.

Were cells detected?

State if the infused cells were detected by the relevant technique.

CONTRIBUTORS

Chiara Bonini

Carmen Ruiz de Elvira

Lucas Stolarczyk

APPENDIX I

KARNOFSKY SCALE

- 100: Normal, no complaints or evidence of disease
- 90: Able to perform normal activity; minor signs and symptoms of disease
- 80: Able to perform normal activity with effort; some signs and symptoms of disease
- 70: Cares for self, unable to perform normal activity or to do active work
- 60: Requires occasional assistance but is able to care for most of own needs
- 50: Requires considerable assistance and frequent medical care
- 40: Requires special care and assistance; disabled
- 30: Hospitalization indicated, although death not imminent; severely disabled
- 20: Hospitalization necessary; active supportive treatment required, very sick
- 10: Fatal processes progressing rapidly; moribund
- 0: Dead

Schag CC, Heinrich RL, Ganz PA. Karnofsky performance status revisited: Reliability, validity, and guidelines. J Clin Oncology. 1984; 2:187-193

ECOG performance status

- Grade 0: Fully active, able to carry on all pre-disease performance without restriction
- Grade 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
- Grade 2: Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
- Grade 3: Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
- Grade 4: Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
- Grade 5: Dead

Oken MM, Creech RH, Tormey DC et-al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am. J. Clin. Oncol. 1983;5 (6): 649-55.