4000: Cellular Therapy Essential Data Pre-Infusion

This form must be completed for all recipients of cellular therapy (non-HCT) where it is the first indication for treatment (no prior hematopoietic cell transplant), when a cellular therapy event (e.g. DCI, CAR-T) is reported on an HCT follow up form, when cellular therapy (non-HCT) is reported as a new indication following a marrow toxic injury (RITN patient) / non-cellular therapy (e.g. chemotherapy, immunotherapy)

For recipients of hematopoietic cellular transplants, complete the pre-TED form 2400 and Disease Classification F2402.

This form reflects baseline recipient data and indication for a course of cellular therapy. All cellular therapies (non-HCT) are being collected on this form, including indications that reflect donor cellular infusions (DCI/DLI) done post-transplant, now referred to as “post-HCT cellular therapy”. A course of cellular therapy are all infusions given per protocol, or when multiple infusions are given for the same indication using the same product/donor (e.g. post-HCT cellular therapy (DCI/DLI)).

The use of cellular therapy is expanding. Treatment strategies include isolation and transfer of specific stem cell populations, administration of effector cells (e.g. cytotoxic T-cells), induction of mature cells to become pluripotent cells, and reprogramming of mature cells (e.g. CAR T-cells).

Links to sections of form:

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for this form, please click here or reference

the retired manual section on the Retired Forms Manuals webpage.

Date	Manual Section	Add/ Remove/ Modify	Description
8/14/ 2019	4000: Cellular Therapy and HCT History	Modify	Updated instruction for question 24: If “yes”, continue to question 29. If “no”, continue with question 25. If “unknown”, questions 25, 26, and 28 are optional and you can continue to question 23.
8/14/ 2019	4000: Cellular Therapy and HCT History	Modify	Updated instruction for question 15: If “yes”, continue to question 23. If “no”, continue with question 16. If “unknown”, questions 16, 17, 18, and 22 are optional and you can continue to question 23.
6/27/ 19	4000: Cellular Therapy Essential Data Pre-Infusion	Modify	Added additional information to the manual providing specific reporting instructions for commercially available products.
1/17/ 19	4000: Cellular Therapy Essential Data Pre-Infusion	Remove	Removed the following blue note box instruction (struck out below) for questions 250 to 252 functional status. Functional status should be reported for every indication. ~~*These questions are for malignant disease indications or relapsed, persistent, or progressive disease only.*~~
2/15/ 18	4000: Cellular Therapy Essential Data Pre-Infusion	Modify	Removed text (struck out below) and added text (in red below) to the instructions for question 49. ~~If the indication for cellular therapy is relapsed, persistent or progressive disease (post-HCT), the indication should be the primary disease for which the cellular therapy is being given.~~ If the recipient is receiving post-HCT cellular therapy (e.g. DCI/DLI) for relapsed, persistent, or progressive disease, the indication should be recorded as “malignant hematologic disorders” and complete a new F2402 for the disease that has relapsed/persisted/progressed.
2/13/ 18	4000: Cellular Therapy Essential Data Pre-Infusion	Remove	Removed the instruction below from section Q68-93: Disease Assessment at Last Evaluation Prior to Cellular Therapy. *Specify the method(s) of disease detection below. For each method used, if the result was positive report the first date the disease was detected; if the result was negative report the last date the method was used prior to cellular therapy.*
1/30/ 18	4000: Cellular Therapy Essential Data Pre-	Modify	Version 3 of the 4000: Cell Therapy Essential Data Pre-Infusion section of the Forms Instructions Manual released. Version 3 corresponds to revision 5 of the Form 4000.

	Infusion		

Last modified: 2019/08/14

Q1-13: Recipient Data

Recipient Ethnicity and Race
For scenarios where both HCT and CT forms will be submitted at the same time, there are duplicate questions across the F2400 and F4000. To reduce the reporting burden, duplicated questions on the Cellular Therapy forms are disabled. This includes recipient ethnicity and race reported on F4000.

Question 1: Ethnicity

Indicate the recipient's ethnicity. The United States Office of Management and Budget (OMB) has defined ethnicity as culturally or geographically determined. The distinction between Hispanic and non-Hispanic is for the purpose of the United States census. According to the OMB, "Hispanic" is an ethnic designation based upon where someone (his or her ancestors) was raised (e.g., "Latin America"). Hispanic people may be of any race. The CIBMTR recognizes regional differences with regard to the interpretation of ethnicity throughout the world.

If the recipient is not a resident of the USA, select "not applicable."

If the recipient declines to provide this information or the recipient's ethnicity is not documented, select "unknown."

For more information regarding ethnicity, see Appendix I.

Question 2: Race: (check all that apply)

Indicate the recipient's race. If this recipient has reported that they are more than one race, please select all options that apply. The race groups provided are specific to the United States.

For non-U.S. centers, select "not reported" if the rules/regulations of your country prohibit the collection or reporting of race data (or due to lack of documentation). If race is reported, it may be necessary to consult with the recipient to select the race group(s) with which they most closely identify.

If the recipient declines to provide this information, select "not reported." If the recipient's race is not documented, select "unknown."

For more information regarding race, see Appendix I.

Question 3: Has the recipient signed an IRB / Ethics Committee-approved consent form for submitting research data to the CIBMTR?

> **!** To be compliant with Federal Regulations for human research subject protection, centers must obtain IRB-approved informed consent from recipients and donors (if applicable) to allow data submitted to the CIBMTR to be used for observational research. The NMDP/CIBMTR has written protocols and informed consent documents for the Observational Database. All centers must have local IRB approval for the Observational Database protocol. The NMDP IRB has approved these protocols and consent forms, and the documents are provided to participating sites to include with their local IRB submissions. International Centers must obtain consent of each patient participating in the Observational Database in a manner consistent with the laws and regulations of their country.

> **✻ Reporting Consent Status for DCI and Other Post-HCT Cellular Therapies**
> If this form is being completed for a DCI or other post-HCT cellular therapy reported on a Post-TED Form (Form 2450) or Post-HCT Follow-Up Data Form (Form 2100), report "not applicable" for question 3. The consent status will be reported on the Pre-TED Form (Form 2400) and should not be re- reported here. If the recipient's consent status has changed since the Pre-TED Form was completed, update the consent status on the Pre-TED Form.

When a recipient consents to participate in the Observational Database, their data are available in the CIBMTR's Observational Research Database and may be used for research. The database includes recipient baseline and outcome data for related and unrelated allogeneic transplants from any cell source and for autologous transplants.

The primary purpose of the Observational Research Database is to have a comprehensive source of data that can be used to study hematopoietic cellular transplantation and cellular therapy. Studies using these data include:

- How well recipients recover from their infusions
- How recovery after infusion can be improved
- What the long-term outcomes are after transplantation and cellular therapies
- How access to transplantation for different groups of recipients can be improved
- How well donors recover from collection procedures
- The application and success of transplantation in the management of marrow toxic injuries
- Cellular therapy
- Better understand new complications seen with infusion of certain cellular therapy products
- Compare outcomes of transplantation and cellular therapies between each other and to other therapies

Indicate if the recipient has signed an IRB-approved consent form to participate in the Observational Research Database. If “yes (patient consented),” continue with question 4. If “no” (patient declined)”, “not approached”, or “not applicable” (post-HCT scenario) continue with question 5. If the patient declines consent, any data reported will not be used in observational studies.

When to use the “Not Approached” option for the Research Database Consent
CIBMTR expects all transplant centers to approach all patients for the Research Database consent. The “not approached” option should only be used in the rare event when the physician feels it would be in the best interest of the patient not to be consented.

Question 4: Date form was signed:

Report the date (YYYY-MM-DD) the research database consent form was signed by the recipient. Do not report the date that the witness or healthcare professional signed the consent form.

Question 5: Is the recipient participating in a cellular therapy clinical trial?

Indicate if the recipient is a registered participant with BMT-CTN, RCI-BMT, USIDNET, COG, a Corporate / Industry trial, EudraCT, UMIN, an investigator initiated trial and/or another clinical trial sponsor, **regardless if that sponsor uses CIBMTR forms to capture outcomes data**. If “yes,” continue with question 6 to report the sponsor. If “no,” continue with question 12. If the participant is enrolled in multiple studies, even if from the same sponsor, report each study separately.

Products that are commercially available are no longer under a clinical trial.

- BMT-CTN: Blood and Marrow Transplant Clinical Trials Network
- RCI-BMT: Resource for Clinical Investigation in Blood and Marrow Transplant
- USIDNET: United States Immunodeficiency Network
- COG: Children’s Oncology Group
- Corporate / Industry
- EudraCT: European Clinical Trials Database
- UMIN: University Hospital Medical Information Network Center
- Investigator initiated

Questions 6-11 Reporting Participation in More Than One Study
FormsNet3^{SM} application: Complete questions 6-11 for each study the recipient is participating in by adding an additional instance in the FormsNet^{SM} application.

Paper form submission: Copy questions 6-11 and complete for each study the recipient is participating in.

Question 6 – 11: Study sponsor:

Select the study sponsor of the clinical trial the recipient is participating in. See question 5 for a link to more information about each organization.

If the study sponsor is reported as “BMT-CTN”, “COG”, “Investigator initiated”, “RCI-BMT”, or “USIDNET”, specify the ClinicalTrials.gov identification number in question 11. See links listed under question 5 for more information. Investigator initiated trials include those that are initiated and managed by a non-pharmaceutical/company researcher (e.g. individual physicians or cooperative groups) and center specific trials or multi-center trials. Continue with question 14.

If the recipient is participating in corporate / industry sponsored trial, indicate the study sponsor as “Corporate/Industry” in question 6, specify the name of the Corporate or Industry sponsor in question 7 and report the clinicaltrials.gov ID number in question 11. Corporate/Industry examples include, but are not limited to, Atara Biotherapeutics, Bellicum Pharmaceuticals, BlueBird Bio, Celgene, Juno Therapeutics, Kite Pharma, Mesoblast, and Novartis. Continue with question 14.

If the recipient is participating in a European Medicines Agency clinical trial, indicate the study sponsor as “EudraCT” in question 6 and specify the Study identification number in question 8 (not the recipient ID). The European Union Drug Regulating Authorities Clinical Trials is the European Clinical Trials Database of all clinical trials of investigational medicinal products with at least one site in the European Union commencing 1 May 2004 or later. See link listed under question 5 for more information. The EudraCT number has the format YYYY-NNNNNN-CC, where YYYY is the year in which the number is issued, NNNNNN is a six digit sequential number, and CC is a check digit. Continue with question 12.

If the recipient is participating in a study with UMIN, indicate the study sponsor as “UMIN” in question 6 and specify the alpha-numeric Study identification number in question 9 (not the recipient ID). UMIN was established in 1989 as a cooperative organization national medical school in Japan, sponsored by the Ministry of Education, Culture, Science, Sports and Technology (MEXT), Japan. See link listed under question 5 for more information. Continue with question 12.

If the recipient is participating in a clinical trial and the study sponsor is not listed, select “other sponsor” in question 6, specify the sponsor name in question 10, and report the ClinicalTrials.gov identification number in question 11. Continue with question 14.

ClinicalTrials.gov Identification Number
All clinical trials are required to be registered on the clinicaltrials.gov website and will have an associated identification number. Report the number in question 11, excluding the letters "NCT" that precede the digits.

Question 12: Is the recipient receiving cellular therapy outside of the context of a clinical trial?

Indicate "yes" if the recipient is receiving cellular therapy in the setting of "institutional guidelines/standard of care", "hospital exemption", or "compassionate use" and continue with question 13 (see below for definitions). If "no", continue with question 14.

Question 13: Specify the reason for not being on a clinical trial: (check all that apply)

Institutional guidelines/standard of treatment: internal protocols at the center

Hospital exemption: applicable when giving cell therapy product without a clinical trial, the hospital that produces the cells must be the hospital that gives the cells.

Compassionate use: No protocol is available or approved by institution, the physician asks for a one- time use

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Q14-28: Cellular Therapy and HCT History

Question 14: Is this the first application of cellular therapy (non-HCT)?

Indicate if this is the recipient's first cellular therapy application. "First application" is defined as the first application the recipient ever receives, not the first application the recipient receives at your facility. The intent is to capture the full picture of the recipient's treatment history.

If "yes" or "unknown", continue with question 23. If "no", continue with question 15.

Question 15: Were all prior cellular therapies (non-HCT) reported to the CIBMTR?

This should include any/all infusions not performed at your center. If the recipient is a transfer patient, you will be able to see all past infusion dates in the Recipient Information Grid in FormsNet3^{SM}. Contact the CIBMTR Customer Service Center if there are questions.

If "yes", continue to question 23. If "no", continue with question 16. If "unknown", questions 16, 17, 18, and 22 are optional and you can continue to question 23.

Question 16: Specify the number of prior cellular therapies:

Enter the number of prior cellular therapies for the recipient. A "cellular therapy event" is defined as the infusion or administration of a cellular therapy product for treatment of a specific indication(s). Each infusion or administration of a cellular product should be counted separately. Include all infusions the recipient received, even if they were not performed at your center. The intent is to capture the full picture of the recipient's treatment history.

Questions 17-22 Reporting Prior Cellular Therapies
FormsNet3^{SM} application: Complete questions 17-22 to report all prior cellular therapies that have not yet been reported to the CIBMTR by adding an additional instance in the FormsNet3^{SM} application.
Paper form submission: Copy questions 17-22 and complete for each prior cellular therapy that has not yet been reported to the CIBMTR.

Question 17: Date of the prior cellular therapy:

Report the date (YYYY-MM-DD) of the prior cellular therapy being reported in this instance. If the exact date is unknown and must be estimated, check the "date estimated" box.

For more information regarding reporting partial or unknown dates, see General Instructions, General Guidelines for Completing Forms.

Question 18: Was the cellular therapy performed at a different institution?

Indicate if the prior cellular therapy being reported in this instance was performed at another institution. If “yes”, report the name and address of the institution in question 19. If “no”, continue with question 20.

Question 19: Specify the institution that performed the prior cellular therapy:

Report the name, city, state, and country of the institution where the recipient’s prior cellular therapy being reported in this instance was performed. These data are used to identify and link the recipient’s existence in the database and, if necessary, obtain data from the other institution where the previous treatment was administered.

Question 20 & 21: Specify the indication for the prior cellular therapy:

Select the indication for the prior cellular therapy being reported in this instance. Any indication that is followed by “(post-HCT)” or “(with HCT)” requires that a prior HCT also be reported to CIBMTR.

If the indication for the prior cellular therapy is not listed, select “other indication” and specify the indication in question 21. If the indication for the prior cellular therapy is not documented, select “unknown”.

Question 22: What was the cell source for the prior cellular therapy? (check all that apply)

Indicate the cell source(s) for the prior cellular therapy being reported in this instance. If the product is “off the shelf” or a “third party donor” product obtained from pharmaceutical companies or other corporate entities, donor type should still be identified

An autologous product has cells collected from the recipient for his/her own use.

An unrelated donor (allogeneic, unrelated) is a donor who shares no known ancestry with the recipient. Include adoptive parents/children or step-parents/children.

A related donor (allogeneic or syngeneic, related) is a blood-related relative. This includes monozygotic (identical twins), non-monozygotic (dizygotic, fraternal, non-identical) twins, siblings, parents, aunts, uncles, children, cousins, half-siblings, etc.

Questions 23-28 HCT History
For scenarios where both HCT and CT forms will be submitted at the same time, there are

duplicate questions across the F2400 and F4000. To reduce the reporting burden, duplicated questions on the Cell Therapy forms are disabled. This includes HCT History reported in Q23-28.

Question 23: Has the recipient ever had a prior HCT?

Include all HCTs in the recipient's history, even if the transplants were not performed at your center. The intent is to capture the full picture of the recipient's treatment history.

If "yes" continue with question 24. If "no" or "unknown", continue with question 29.

Question 24: Were all prior HCTs reported to the CIBMTR?

This should include any/all HCTs not performed at your center. If the recipient is a transfer patient, you will be able to see all past infusion dates in the Recipient Information Grid in FormsNet3SM. Contact your CIBMTR CRC if there are questions.

If "yes", continue with question 29. If "no", continue with question 25. If "unknown", questions 25, 26, and 28 are optional and you can continue to question 29.

Question 25: Date of the prior HCT:

Report the date (YYYY-MM-DD) of the prior HCT being reported in this instance.

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 26: Was the HCT performed at a different institution?

Indicate if the prior HCT being reported in this instance was performed at another institution. If "yes" report the name and address of the institution in question 27. If "no" continue with question 28.

Question 27: Specify the institution that performed the prior HCT:

Report the name, city, state, and country of the institution where the recipient's prior HCT being reported in this instance was performed. These data are used to identify and link the recipient's existence in the database and, if necessary, obtain data from the previous transplant center.

Question 28: Specify the HSC source(s) for the prior HCT: (check all that apply)

Indicate the applicable cell source(s) for the prior HCT being reported in this instance.

An autologous product has cells collected from the recipient for his/her own use.

An unrelated donor (allogeneic, unrelated) is a donor who shares no known ancestry with the recipient. Include adoptive parents/children or step-parents/children.

A related donor (allogeneic, related) is a blood-related relative. This includes monozygotic (identical twins), non-monozygotic (dizygotic, fraternal, non-identical) twins, siblings, parents, aunts, uncles, children, cousins, half-siblings, etc.

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Q29-46: Product Identification

Question 29: Specify the total number of products: (per protocol) (as part of this course of cellular therapy)

Report the number of products to be infused per protocol. This question is used to make the correct number of Cellular Therapy Product forms (Form 4003) come due. Each product must be part of the protocol and will be given regardless of disease response.

Example 1. A series of collections from the same donor that uses the same collection method and mobilization cycle, even if the collections are performed on different days, should be considered a single cellular therapy product if only one set of manufacturing steps are applied to the collected material.

Example 2. Products from the same donor but obtained using different manufacturing steps are considered different products and require multiple product forms.

Example 3. If the cells were manipulated or modified by different methods and at the end of the manufacturing process are combined for a single infusion or administration, it will be considered a single product and it will require a single Form 4003.

Question 30: Is the product genetically modified?

Genetically modified products include any product that was manipulated to alter its gene expression through the insertion of different genes, or editing of genes. An example of a genetically modified product is the manipulation of T-lymphocytes to express Chimeric Antigen Receptors (CAR T-cells) directed towards specific tumor targets (antigens). If more than one product is being infused, indicate if any of the products are genetically modified. This question is used to determine the follow up schedule of the cellular therapy.

Questions 31-43 Reporting Donor Information
FormsNet3^{SM} application: Complete questions 31-43 to report all donors, per protocol, used for the products reported in question 29 by adding an additional instance in the FormsNet3^{SM} application.
Paper form submission: Copy questions 31-43 and complete for all donors, per protocol, used for the products reported in question 29.

Question 31: Specify the cell source:

Select the cell source for the donor being reported in this instance. If the product is “off the shelf” or a “third

party donor" product obtained from pharmaceutical companies or other corporate entities, donor type should still be identified.

An autologous product has cells collected from the recipient for his/her own use. Continue with question 34.

An unrelated donor (allogeneic, unrelated) is a donor who shares no known ancestry with the recipient. Include adoptive parents/children or step-parents/children. Continue with question 33.

A related donor (allogeneic, related) is a blood-related relative. This includes monozygotic (identical twins), non-monozygotic (dizygotic, fraternal, non-identical) twins, siblings, parents, aunts, uncles, children, cousins, half-siblings, etc. Continue with question 32.

Question 32: Specify the related donor type:

Indicate the relationship and match between the recipient and the related donor being reported in this instance.

Syngeneic:
Includes: Monozygotic (identical) twins. Occurs when a single egg is fertilized to form one zygote, which then divides into two separate embryos.
Does not include: Other types of twins or HLA-identical siblings (see below).

HLA-identical sibling:
Includes: Non-monozygotic (dizygotic, fraternal, non-identical) twins. Occurs when two eggs are fertilized by two different sperm cells at the same time. This category also includes siblings who aren't twins, but have identical HLA types. The patient and donor will be allele-level matched at HLA-A, B, C, and DRB-1.
Does not include: Half-siblings should be reported as "HLA matched other relatives" if their HLA typing is a match, or "mismatched relative" if it does not match.

HLA-matched other relative:
Includes: All blood-related relatives, other than siblings, who are HLA matched (e.g., parents, aunts, uncles, children, cousins, half-siblings). The patient and donor will be allele-level matched at HLA-A, B, C, and DRB-1.
Does not include: Adoptive parents/children or step-parents/children who are HLA matched.

HLA-mismatched relative:
Includes: Siblings who are not HLA-identical and all other blood-related relatives who have at least one HLA mismatch (mismatch can be at the antigen or allele level) (e.g., parents, aunts, uncles, children, cousins, half-siblings). The patient and donor will be allele-level mismatched at one or more loci (HLA-A, B, C, or DRB-1).

Does not include: Adoptive parents/children or stepparents/children.

Question 33: Was this donor used for any prior cellular therapies or HCT? (for this recipient)

Indicate if the allogeneic unrelated or related donor being reported in this instance was used for prior cellular therapies or HCT for this recipient. Do not answer this question for autologous donors.

> ✻ Questions 34-37 allow for the selection of multiple tissue sources and cell types for a product. For example, if the product consists of two different types of lymphocytes, the source of cells will be peripheral blood and the cell types will be CD4+ and CD8+ lymphocytes. Also, in the case of a tumor vaccine, the sources will be tumor and peripheral blood and the cell type will be dendritic cells/tumor cell hybridomas.

Question 34-35: What is the tissue source of the cellular product? (check all that apply)

> ✻ For commercially available products Kymriah® and Yescarta®, report the tissue source as "peripheral blood".

Select from the list the tissue source(s) of the cellular product being reported in this instance. If the source is selected as 'Other tissue source', specify the other source in question 35 and continue with question 36.

Question 36-37: What is the cell type? (check all that apply)

> ✻ For commercially available products Kymriah® and Yescarta®, report the cell type as "Lymphocytes (unselected)".

Select from the list the cell type(s) of the cellular product being reported in this instance. This should be the type of cell(s) harvested to make the product and / or in the product infused. If the cell type is selected as 'Other cell type', specify the other cell type in question 37 and continue with question 38. All cell types selected here must also be reported on the Cellular Therapy Infusion Form 4006. Please refer to the 4006 Manual, Q17-45, for description of cell types.

Question 38-43: Where was the cellular therapy product manufactured / processed?

> ✻ For the commercially available product **Kymriah®**, report the manufacturing information as follows:
> Question 38: "Pharmaceutical / biotech company"

Question 40: “Novartis”
Question 42: “Tisagenlecleucel (Kymriah®)”

For the commercially available product **Yescarta®**, report the manufacturing information as follows:
Question 38: “Pharmaceutical / biotech company”
Question 40: “Kite Pharma”
Question 42: “Axicabtagene Ciloleucel (Yescarta®)”

If the product is from an NMDP donor used for a prior HCT, report that the product was manufactured by a “Cell processing laboratory at the same center as the product is being infused,” and continue with question 44.

If the product was manufactured by a pharmaceutical or biotech company, continue with question 40 and select the **pharmaceutical or biotech company** from the list. If the company is not in the dropdown list, select ‘other pharmaceutical company’ and report the name and location of the company in question 41.

If the company has a commercially available product, select the product name in question 42. If the product name is not in the list, select ‘other product’ and report the name in question 43.

If the product was manufactured by a **cell processing laboratory off site** that is not a pharmaceutical / biotech company, continue with question 41 and report the name and location of the laboratory. Continue with question 44.

If the product was manufactured by a **cell processing laboratory at the same center as the product is being infused**, continue with question 44.

If the product was manufactured by another site not listed above, continue with question 39 to specify the other site and report the name and location in question 41.

Question 44: Is a subsequent HCT part of the overall treatment protocol?

This question intends to capture instances where the cellular therapy is administered in association with a HCT, either planned or dependent upon the response to the cellular therapy. If a subsequent HCT is part of the overall treatment plan, indicate “yes”, continue with question 45. If “no”, continue with question 47.

Question 45: Specify the HCT type:

Specify the type of the subsequent HCT that is planned as part of the overall treatment protocol.

An autologous product has cells collected from the recipient for his/her own use.

An allogeneic product is from a donor who is not the recipient, either related or unrelated to the recipient.

Question 46: Specify the circumstances which the subsequent HCT will be performed:

Specify the reason for which the subsequent HCT will be performed as “regardless of response to cellular therapy”, “only if the patient responds to cellular therapy” or “only if the patient fails to respond or has an incomplete response”.

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Q47-60: Indication for Cellular Therapy

Question 47-48: Is the cellular therapy being given for prevention?

Reasons for prevention include:

- GVHD prophylaxis (with HCT)
- Prevent disease relapse (post-HCT)
- Infection prophylaxis

If the indication is any in the list above and the cell therapy is being given with HCT or post-HCT, no additional consent is required from the patient:

Question 49: What was the indication for performing treatment with cellular therapy?

From the list provided, select the indication for which the recipient is receiving the cellular therapy.

If the indication is any in the list below and the cell therapy is being given with HCT or post-HCT, no additional consent is required from the patient:

- Suboptimal donor chimerism (post-HCT)
- Immune reconstitution (post-HCT)
- GVHD treatment (post-HCT)

The Disease Classification Form 2402 will come due if the indication is reported as “malignant hematologic disorder”, “non-malignant disorder”, or “solid tumor”. This allows CIBMTR to capture disease specific information for cellular therapy utilizing an existing form to maintain consistency in data collection.

If the recipient is receiving post-HCT cellular therapy (e.g. DCI/DLI) for relapsed, persistent, or progressive disease, the indication should be recorded as “malignant hematologic disorders” and complete a new F2402 for the disease that has relapsed/persisted/progressed.

Disease Classification Questions
The newest versions of the TED forms use the World Health Organization (WHO) disease classifications. The disease classification questions contain all of the established WHO disease types and subtypes. The “other indication” category should be used only if the recipient’s disease is not one of the listed options. For more information regarding disease classification, consult a transplant physician, contact the CIBMTR Customer Service Center,

or visit the WHO website.

Malignant vs. Non-Malignant
Malignant disease involve cells dividing without control that can spread to other parts of the body through blood and lymph systems. These diseases are usually characterized by unlimited, aggressive growth, invasion of surrounding tissues, and metastasis. Non-malignant tumors involve cell overgrowth, but lack the malignant properties of cancer. Non-malignant diseases include severe aplastic anemia, disorders of the immune system, inherited disorders of metabolism, etc. The CIBMTR database disease codes are represented in parentheses after the disease subtype on the Disease Classification questions and can be helpful in mapping diagnosis [e.g Myeloid Sarcoma (295)], and determining if the disease is malignant or non-malignant. Disease codes (10-299) indicate a malignant disease, with the exception of Paroxysmal Nocturnal Hemoglobinuria (PNH) (56). A disease code of (300) or above indicates a non- malignant disease, with the exception of disease code (900), which could indicate either a malignant or non-malignant disease.

Question 50: Date of diagnosis:

This question is answered if the indication for cellular therapy is cardiovascular disease, musculoskeletal disease, neurologic disease, ocular disease, pulmonary disease, infection treatment or other indication. The diagnosis date for malignant hematologic disorder, non-malignant disorder or solid tumor will be captured on the Disease Classification Form (Form 2402).

Report the date (YYYY-MM-DD) of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease for which the patient is receiving cellular therapy. Enter the date the sample was collected for examination. If the indication is infection, report the date of diagnosis as the collection date for the first positive microbiology culture. If the diagnosis was determined at an outside center, and no documentation of a pathological or laboratory assessment is available, the dictated date of diagnosis within a physician note may be reported. Do not report the date symptoms first appeared.

If the recipient was diagnosed prenatally (in utero) or if the indication is a congenital disorder, report the date of birth as the date of diagnosis.

If the exact pathological diagnosis date is not known, use the process described in General Instructions, General Guidelines for Completing Forms.

Question 51-53: Specify cardiovascular disease:

If cardiovascular disease is the indication for cellular therapy, indicate the specific disease in question 51. If “other cardiovascular disease” is selected, specify in question 52. If “other peripheral vascular disease” is

selected, specify in question 53. Continue with question 94.

Question 54-55: Specify musculoskeletal disorder:

If musculoskeletal disorder is the indication for cellular therapy, indicate the specific disorder in question 54. If “other musculoskeletal disorder”, specify in question 55. Continue with question 94.

Question 56-57: Specify neurologic disease:

If neurologic disease is the indication for cellular therapy, indicate the specific disease in question 56. If “other neurologic disease”, specify in question 57. Continue with question 94.

Question 58: Specify ocular disease

If ocular disease is the indication for which the recipient is receiving the cellular therapy, specify in question 58. Examples include treatment of glaucoma or photoreceptor degeneration. Continue with question 94.

Question 59: Specify pulmonary disease

If pulmonary disease is the indication for which the recipient is receiving the cellular therapy, specify in question 59. Examples include Chronic Obstructive Pulmonary Disease (COPD) or pulmonary fibrosis. Continue with question 94.

Question 60: Specify other indication

If the indication for which the recipient is receiving the cellular therapy is “other indication” because it does not fit into a category listed above, specify the indication in question 60. An example is treatment of autism by cellular therapy. Contact your CIBMTR CRC if there is a question on the indication. Continue with question 94.

Last modified: 2019/06/27

Q61-67: Infection

This section to be completed when infection is the indication for the cellular therapy.

Question 61-67: Organism:

If treatment of infection is the indication for the cellular therapy, report the fungal or viral organism(s) for which the recipient is receiving the cellular therapy.

Organism:
From Table 1 entitled “Codes for Commonly Reported Organisms”, select the code corresponding to the identified organism as indicated on the microbiology report, laboratory report, or other physician documentation. Report the code in the boxes provided on the form.

Fungal infections: Note the inclusion of Pneumocystis (formerly found under parasites). The most commonly found fungal infections are Candida (*C. albicans*), Aspergillus (*A. fumigatus*), and *Fusarium sp.*

Viral infections: Caused by exposure to a new virus or reactivation of a dormant virus already present in the body. The most common viral infections are due to HSV (Herpes Simplex Virus), and CMV (Cytomegalovirus). If the site of CMV is the lung, confirm whether the patient had interstitial pneumonitis rather than CMV pneumonia.

Table 1: Codes for Commonly Reported Organisms

201 *Candida albicans*	301 Herpes Simplex Virus (HSV)	323 Influenza A Virus
208 Candida non-albicans	302 Varicella Virus	324 Influenza B Virus
210 *Aspergillus*, NOS	303 *Cytomegalovirus* (CMV)	325 Enterovirus (ECHO, Coxsackie)
211 *Aspergillus flavus*	304 *Adenovirus*	326 Enterovirus (polio)
212 *Apergillus fumigatus*	306 Hepatitis A Virus	327 Enterovirus D68 (EV-D68)
213 *Aspergillus niger*	307 Hepatitis B Virus	328 Enterovirus NOS
214 *Aspergillus ustus*	308 Hepatitis C Virus	340 Hepatitis E
215 *Aspergillus terreus*	309 Human Immunodeficiency Virus 1 or 2	341 BK Virus
221 *Cryptococcus*	310 Influenza, NOS	342 JC Virus (Progressive Multifocal

neoformans		Leukoencephalopathy (PML))
222 *Cryptococcus gattii*	311 Measles Virus (Rubeola)	343 Human metapneumovirus
230 *Fusarium* (all species)	312 Mumps Virus	344 *Coronavirus*
240 *Zygomycetes*, NOS	314 Respiratory Syncytial Virus (RSV)	345 *Norovirus*
241 *Mucorales* (all species)	315 Rubella Virus	346 Dengue Virus
242 *Rhizopus* (all species)	316 Human Parainfluenza Virus (all species)	347 Chikaugunya virus
260 *Pneumocystis* (PCP / PJP)	317 Human herpesvirus 6 (HHV-6)	348 West Nile Virus (WNV)
261 *Histoplasma* (capsulatum)	318 Epstein-Barr Virus (EBV)	349 Human T-lymphotropic Virus 1 or 2
270 *Blastomyces* (dermatitidis)	320 *Rotavirus* (all species)	503 Suspected fungal infection
271 *Coccidioides* (all species)	321 *Rhinovirus* (all species)	777 Other organism
272 *Scedosporium* (all species)	322 *Human Papillomavirus* (HPV)	

Last modified: 2018/01/30

Q68-93: Disease Assessment at Last Evaluation Prior to Cellular Therapy

Disease Assessment
These questions are for malignant disease indications with relapsed, persistent or progressive disease only. This section should not be completed if the indication for cellular therapy is reported as one of the following:
*Suboptimal donor chimerism (post-HCT)
*Immune reconstitution (post-HCT)
*GVHD prophylaxis (with HCT)
*GVHD treatment (post-HCT)
*Prevent disease relapse (post-HCT)
*Infection treatment
*Infection prophylaxis

All values reported in questions 68-93 must reflect the most recent testing prior to the start of systemic therapy / preparative regimen (or infusion if no preparative regimen was given). If testing was not performed dear the start of the systemic therapy / preparative regimen / infusion (within approximately 30 days) and after the most recent line of therapy (if applicable), report “Unknown” for that disease assessment.

Question 68: Was the disease assessed prior to the cellular therapy?

Indicate if the disease status was assessed prior to the cellular therapy. If “yes”, continue with question 69. If “no”, continue with question 94.

Method of Disease Assessment:
This section should be completed for every malignant disease. Not all diseases have molecular and / or cytogenetic / FISH abnormalities to monitor disease status. If a disease assessment was done, but has always been normal, report the disease status as “not applicable”. In some circumstances, disease may be detected by molecular or cytogenetic testing, but may not be considered a relapse or progression. Test results should still be reported.

Question 69: Was the disease status assessed by molecular testing (e.g. PCR)?

Molecular assessment involves testing blood, bone marrow, tumor or other source for the presence of known molecular markers. Molecular assessments are the most sensitive test for genetic abnormalities and involve amplifying regions of cellular DNA by polymerase chain reaction (PCR), typically using RNA to

generate complementary DNA through reverse transcription (RT-PCR). The amplified DNA fragments are compared to a control, providing a method of quantifying log increase of genetic mutation transcripts. Each log increase is a 10-fold increase of gene transcript compared to control. RFLP testing (with PCR amplification) is an example of a molecular test method used to detect BCR/ABL.

Report “yes” if a molecular method was used to determine disease status at the last evaluation prior to cellular therapy and continue with question 70. If a molecular method was not used to determine disease status, check “no” and continue with question 73.

Report “not applicable” if molecular studies were never performed (since diagnosis) or have never shown abnormalities associated with the recipient’s primary disease for transplant and continue with question 73.

Report “no” if a molecular testing was not performed or could not be used to determine disease status and continue with question 73.

Question 70: Date sample collected:

Indicate the date (YYYY-MM-DD) the sample was collected for disease assessment by molecular method. The sample collection date should be prior to the start of any systemic therapy given immediately prior to the cellular therapy infusion (the date reported in question 95).

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 71: Was disease detected?

Report whether the recipient’s primary disease was detected by molecular testing on the date reported in question 70. In order to be considered positive for disease, the assay must detect a number of copies of the molecular marker exceeding the threshold for sensitivity of the assay, for a quantitative study. However, do note that the presence of only a single marker amongst numerous tested is sufficient to indicate disease detected.

If the recipient’s primary disease was detected by the molecular assessment reported in question 70, report “yes” and continue with question 72.

If the recipient’s primary disease was not detected by the molecular assessment reported in question 70, report “no” and continue with question 73.

Question 72: Was the status considered a disease relapse or progression?

If the physician believes the test results indicate disease relapse or progression, report “yes.” If the recipient

has a positive test result, but the physician does not believe the result represents relapse or progression (e.g., a recipient transplanted for CML exhibits such a low level of BCR-ABL positivity post-cellular therapy that the physician does not believe is disease), report “no”.

Question 73: Was the disease status assessed via flow cytometry (immunophenotyping)?

Flow cytometry is a technique that can be performed on blood, bone marrow, or tissue preparations where cell surface markers can be quantified on cellular material.

Report “yes” if flow cytometry was used to determine disease status at the last evaluation prior to cellular therapy and continue with question 74.

Report “not applicable” if flow cytometry was never performed (since diagnosis) or has never shown abnormalities associated with the recipient’s primary disease for transplant and continue with question 77.

Report “no” if flow cytometry was not performed or could not be used to determine disease status and continue with question 77.

Question 74: Date sample collected:

Indicate the date (YYYY-MM-DD) the sample was collected for disease assessment by flow cytometry. The sample collection date should be prior to the start of any systemic therapy given immediately prior to the cellular therapy infusion (the date reported in question 95).

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 75: Was disease detected?

Report whether the recipient’s primary disease was detected by flow cytometry on the date reported in question 74. In order to be considered positive for disease, an abnormal cell population associated with the recipient’s primary transplant disease must be detected regardless of the sensitivity of the flow cytometry panel performed. This means an abnormal cell population detected by MRD flow cytometry would be reported in the same way as an abnormal cell population detected by a standard flow cytometry assay.

If the recipient’s primary disease was detected by the flow cytometry assessment reported in question 74, report “yes” and continue with question 76.

If the recipient’s primary disease was not detected by the flow cytometry assessment reported in question 74, report “no” and continue with question 77.

Question 76: Was the status considered a disease relapse or progression?

If the physician believes the test results indicate disease relapse or progression, report “yes.” If the recipient has a positive test result, but the physician does not believe the result represents relapse or progression, report “no.”

Question 77: Was the disease status assessed by cytogenetic testing (karyotyping or FISH)?

Cytogenetic studies involve the study of chromosomes, typically through one of two methods: karyotyping or fluorescence in situ hybridization (FISH). Blood, bone marrow, or tissue preparations may be tested by either of these two methods. Karyotyping is both less sensitive and less specific than FISH testing; FISH studies identify only abnormalities detectable by the employed probe set, and cannot provide information about the presence or absence of chromosomal abnormalities or markers outside the specific probe set utilized. Although often used for finding specific features in DNA, FISH is not as sensitive as molecular methods, even though the markers identified may be the same. For more information of cytogenetic assessments, see Appendix C.

Report “yes” if cytogenetic testing was used to determine disease status at the last evaluation prior to cellular therapy and continue with question 78.

Report “not applicable” if cytogenetic testing was never performed (since diagnosis) or has never shown abnormalities associated with the recipient’s primary disease for transplant and continue with question 86.

Report “no” if cytogenetic testing was not performed or was not used to determine disease status and continue with question 86.

Question 78: Was the disease status assessed by karyotyping?

Karyotyping is performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

Report “yes” if karyotyping was used to determine disease status at the last evaluation prior to cellular therapy and continue with question 79.

Report “not applicable” if karyotyping was never performed (since diagnosis) or has never shown abnormalities associated with the recipient’s primary disease for transplant and continue with question 82.

Report “no” if karyotyping was not performed or was not used to determine disease status and continue with question 82.

Question 79: Date sample collected:

Indicate the date (YYYY-MM-DD) the sample was collected for disease assessment by karyotyping. The sample collection date should be prior to the start of any systemic therapy given immediately prior to the cellular therapy infusion (the date reported in question 95).

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 80: Was disease detected?

Report whether the recipient's primary disease was detected by karyotyping on the date reported in question 79. Do not include clinically insignificant polymorphism, or chromosomal abnormalities of no known significance as disease detected. This includes anomalies such as age-dependent loss of the chromosome Y.

If the recipient's primary disease was detected by the karyotyping assessment reported in question 79, report "yes" and continue with question 81.

If the recipient's primary disease was not detected by the karyotyping assessment reported in question 79, report "no" and continue with question 82.

Question 81: Was the status considered a disease relapse or progression?

If the physician believes the test results indicate disease relapse or progression, report "yes". If the recipient has a positive test result, but the physician does not believe the result represents relapse or progression, report "no."

Question 82: Was the disease status assessed by FISH?

Fluorescence in situ hybridization (FISH) studies identify only abnormalities detectable by the employed probe set, and cannot provide information about the presence or absence of chromosomal abnormalities or markers outside the specific probe set utilized.

Report "yes" if FISH was used to determine disease status at the last evaluation prior to cellular therapy and continue with question 83.

Report "not applicable" if FISH studies were never performed (since diagnosis) or have never shown abnormalities associated with the recipient's primary disease for transplant and continue with question 86.

Report "no" if FISH studies were not performed or used to determine disease status and continue with

question 86.

Question 83: Date sample collected:

Indicate the date (YYYY-MM-DD) the sample was collected for disease assessment by FISH. The sample collection date should be prior to the start of any systemic therapy given immediately prior to the cellular therapy infusion (the date reported in question 95).

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 84: Was disease detected?

If the recipient's primary disease was detected by the FISH assessment reported in question 83, report "yes" and continue with question 85.

If the recipient's primary disease was not detected by the FISH assessment reported in question 83, report "no" and continue with question 86.

Question 85: Was the status considered a disease relapse or progression?

If the physician believes the test results indicate disease relapse or progression, report "yes". If the recipient has a positive test result, but the physician does not believe the result represents relapse or progression, report "no".

Question 86: Was the disease status assessed by radiological assessment? (e.g., PET, MRI, CT)

Radiologic assessments are imaging techniques used to assess disease response to transplant, typically for lymphomas or solid tumors, though valuable in some less common presentations of disease, such as leukemia cutis. Imaging techniques used to evaluate disease response typically include PET, CT, or MIBG, but may include x-ray, skeletal survey, or ultrasound in some cases.

Report "yes" if a radiologic assessment was used to determine disease status at the last evaluation prior to cellular therapy and continue with question 87.

Report "not applicable" if radiologic assessments were never performed (since diagnosis) or have never shown abnormalities associated with the recipient's primary disease for transplant and continue with question 89.

Report "no" if a radiologic assessment was not performed or used to determine disease status and continue with question 89.

Question 87: Date assessed:

Indicate the date (YYYY-MM-DD) the disease was assessed by radiological assessment. The sample collection date should be prior to the start of any systemic therapy given immediately prior to the cellular therapy infusion (the date reported in question 95).

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 88: Was disease detected?

If the recipient's primary disease was detected by the radiologic assessment reported in question 87, report "yes".

If the recipient's primary disease was not detected by the radiologic assessment reported in question 87, report "no".

Question 89: Was the disease status assessed by clinical / hematologic assessment?

Clinical / hematologic assessments are the least sensitive method of disease detection. Examples include circulating blasts in the bloodstream for AML or enlargement of a malignant mass for lymphoma / solid tumor as determined by physical exam. Every recipient who has an evaluation by a physician has a "clinical" assessment.

Report "yes" if a clinical / hematologic assessment was used to determine disease status at the last evaluation prior to cellular therapy and continue with question 90.

Report "no" if a clinical / hematologic assessment was not performed or used to determine disease status and continue with question 92.

Question 90: Date assessed:

Indicate the date (YYYY-MM-DD) the disease was assessed by clinical/hematologic assessment. The sample collection date should be prior to the start of any systemic therapy given immediately prior to the cellular therapy infusion (the date reported in question 95).

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 91: Was disease detected?

If the recipient's primary disease was detected by the clinical / hematologic assessment reported in question

90, report “yes”.

If the recipient’s primary disease was not detected by the clinical / hematologic assessment reported in question 90, report “no”.

Question 92: What was the recipient’s disease status immediately prior to the cellular therapy?

Indicate the disease status of the primary transplant disease immediately prior to the cellular therapy. Disease response criteria vary by disease, and are outlined in the CIBMTR Forms Instructions Manual.

Question 93: Date assessed:

Indicate the date (YYYY-MM-DD) of the disease status reported in question 92. The date assessed should be prior to the start of any systemic therapy given immediately prior to the cellular therapy infusion (the date reported in question 95).

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

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Q94-249: Systemic Therapy Prior to Cellular Therapy

Question 94: Was systemic therapy given immediately prior to cellular therapy as part of the cellular therapy protocol?

Systemic therapy may include intravenous or oral chemotherapy with the intent to deplete circulating lymphocytes, reduce tumor burden or other reasons. If “yes”, continue with question 95. If “no”, continue with question 250.

If the recipient is receiving a cellular therapy after an HCT, do not report any therapy that was already reported on a Pre-TED F2400. The intent of this question is to capture therapy specific to the cellular therapy infusion.

Question 95: Date started:

Indicate the date (YYYY-MM-DD) the systemic therapy started. This should be the earliest start date of the first drug given.

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 96-97: Specify the reason for which the systemic therapy was given per protocol:

Lympho-depleting therapy: Used to “prime” the patient for optimal CAR T-cell in vivo expansion and antitumor activity. Examples of lympho-depleting therapy include, but not limited to, ATG, Alemtuzumab (Campath) and Cyclophosphamide plus fludarabine.

Reduction of tumor burden: Refers to the reduction of the number of the cancer cells, the size of the tumor or the amount of cancer in the body.

If systemic therapy was given as “Lympho-depleting therapy” or for “Reduction of tumor burden”, continue with question 98. If systemic therapy was given for another reason, select “other reason” and specify in question 97.

Question 98-249: Specify preparative regimen drugs:

> The form lists each drug by the generic name. The form also lists some drugs by broad categories, with specific drugs listed individually. For example, anthracycline is listed as the broad drug category, followed by the specific drugs of daunorubicin, doxorubicin, and idarubicin.

For each drug listed, indicate whether or not it was given as part of the systemic therapy used prior to the cellular therapy infusion. Report the total dose of each drug that was actually given. Do not report the prescribed dose or the daily dose. The pharmacy record or Medication Administration Record (MAR) should be used for determining the exact total dose given.

Some drugs used as part of the systemic therapy regimen are administered with guidance of serum pharmacokinetic testing to determine the recipient's metabolism of the drug. This allows for individual "customization" of the drug dosing to optimize the desired effect and minimize the toxicity.

A common example of this situation occurs in the use of busulfan. In some cases, a "test dose" of the drug is given before the actual systemic therapy regimen is started, and this dose is used for acquiring drug levels that are used to adjust the dose that will be used in the systemic therapy regimen. In other situations, the first dose of the drug is given in the usual fashion as part of the systemic therapy regimen. After this first dose, serum drug levels are drawn and sent to a reference lab. The drug is continued at the starting dose until the lab results are reported and adjustment is made to later doses.

When a drug is used for the systemic therapy regimen where pharmacokinetics will be tested, it is important to distinguish whether the testing will be done with a "test dose" before beginning the preparative regimen or using the first dose of the systemic therapy regimen. The reporting of the dosing for the CIBMTR forms depends upon this distinction. This helps distinguish whether the dose is part of the therapeutic regimen, or not.

1. A test dose was given **> 24 hours** prior to the intended therapeutic dosing.
    - **Example:** A patient with AML underwent a cellular therapy; busulfan and cyclophosphamide were used as the systemic therapy regimen. The patient presented to clinic 9 days before the cellular therapy infusion, where a dose of busulfan at 0.5 mg/kg was given intravenously. Blood samples were drawn for the next 6 hours, after which the patient left the clinic. His samples were sent to a lab, results were returned the next day, and an adjusted dose of busulfan was calculated. He returned to the hospital 6 days before the cellular therapy infusion, and began to receive busulfan at the adjusted dose intravenously for 4 days, followed by cyclophosphamide, and proceeded to receive his cells. Since he received 0.5 mg/kg as a "test dose," this would not be reported in his total systemic therapy regimen dose.

    - If a test dose was given, where the dose was distinct from the therapeutic dosing systemic therapy regimen (often 1-2 or more days prior to the initiation of regular dosing), the start date of the chemotherapy agent should be reported as the date the first therapeutic dose was administered. The actual dose received would NOT include the test dose.

2. The first dose of therapeutic dosing is used for monitoring.
    - **Example:** A patient with ALL underwent a cellular therapy infusion; busulfan and fludarabine were used as the systemic therapy regimen. She was admitted to the hospital 7 days before her cellular therapy infusion, and received a dose of busulfan at 0.8 mg/kg IV at 6:00 AM. Serum samples were drawn every 30 minutes until the next dose of Busulfan at 0.8 mg/kg IV was given at 12:00 noon. Her blood was sent to a reference lab, and she continued to receive busulfan every 6 hours. On day -6, the lab called with her drug levels, and it was determined that the current dose was correct. No adjustment was made, and she completed all 16 doses of busulfan. Since the dose of busulfan (0.8 mg/kg) that was used for drug testing was ALSO her first dose of the preparative regimen, it should be included in the amount of drug that was given for systemic therapy regimen.
        - If the first dose of the systemic therapy regimen was used to determine pharmacokinetics, the start date of the chemotherapy agent should be reported as the date the first dose was administered. The actual dose received would include the dose used for monitoring.

Test doses must be reported consistently at your center. Since most centers follow a consistent approach to pharmacokinetic testing, it should be straightforward for the center to adopt a consistent approach to the reporting of test doses.

For each drug indicated as “yes”:

- Drug doses must be reported in whole numbers. If the total dose includes a decimal, round to the nearest whole number (round up if 0.5 or greater). For paper submission, do not modify the number of boxes or include decimal values.
- Report the date (YYYY-MM-DD) the drug was administered. If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

If monoclonal antibody (mAb) is indicated as “yes”, examples of “other mAb” include Inotuzumab, Daratumomab, and Immune Checkpoint Inhibitors (Pembrolizumab, Nivolumab, and / or Durvalinomab).

The “other drug” category should only be used if the drug is not one of the listed options. If more than one “other” drug is prescribed, list the generic name of the drugs in the space provided **and** attach a copy of the

source document using the attachment feature in FormsNet3^{SM}.

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Q250-252: Functional Status

Specify the functional status of the recipient immediately prior to the cellular therapy.

Question 250: What scale was used to determine the recipient's functional status prior to the cellular therapy?

The CIBMTR uses the Karnofsky/Lansky scale to determine the functional status of the recipient immediately prior to the start of the cellular therapy. The Karnofsky Scale is designed for recipients aged 16 years and older, and is not appropriate for children under the age of 16. The Lansky Scale is designed for recipients one year old to less than 16 years old. For recipients less than one year old, questions 250-252 should be left blank.

Select the appropriate performance scale, Karnofsky or Lansky, based on the recipient's age.

Question 251-252: Performance score prior to the cellular therapy:

Recipient performance status is a critical data field that has been determined to be essential for all outcome-based studies. The CIBMTR uses the Karnofsky/Lansky scale to determine the functional status of the recipient immediately prior to the start of the cellular therapy. For the purposes of this manual, the term "**immediately prior**" represents approximately one month prior to the cellular therapy infusion.

Using the appropriate scale as selected in question 250, select the score (10-100) that best represents the recipient's activity status immediately prior to the start of the preparative regimen. For an example of the Karnofsky / Lansky scale, see Appendix L.

If a Karnofsky / Lansky score is not documented in the source documentation (e.g., inpatient progress note, physician's clinic note), data management professionals should not assign a performance score based on analysis of available documents. Rather, a physician should provide documentation of the performance score.

The CIBMTR recognizes that some transplant centers prefer to collect and use the ECOG performance score as opposed to the Karnofsky / Lansky score. Although the ECOG and Karnofsky / Lansky performance score systems are based on similar principles, the scales are not the same. For example, the Karnofsky / Lansky scale is described in 11 categories, whereas the ECOG performance status is reported in six categories. Due to the overlap between the two systems, an ECOG score of "one" can represent either "80" or "90" on the

Karnofsky / Lansky scale. For centers that collect only an ECOG performance score, CIBMTR will make the following accommodations when auditing the source data: Centers collecting ECOG scores should do so using standard practices to ensure accuracy. For the purposes of CIBMTR reporting, conversion of ECOG to Karnofsky / Lansky should follow a standard and consistent practice. This practice should be clear and reproducible. For more information regarding converting an EGOG score to a Karnofsky / Lansky score, see Appendix L.

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Q253-311: Comorbid Conditions

This section will be answered for malignant hematologic disorders and solid tumor indications only

Question 253: Were there clinically significant co-existing disease or organ impairment at the time of patient assessment prior to preparative regimen?

Hepatic and Renal Comorbidities[1]
In addition to the guidelines listed on the Pre-TED form, include the following time-specific guidelines when reporting hepatic and renal comorbidities
Hepatic Comorbidity: The assessment of liver function tests (ALT, AST and/or Total Bilirubin) has to include at least 2 values per test on two different days within a period extending between day -24 and the start of the systemic therapy regimen. If no systemic therapy was given, then it would be day -24 and the cellular therapy infusion date. If only a single value was reported in this time period, use the most recent test performed between days -40 & -25 as the second value.
Renal (Moderate/Severe) Comorbidity: Serum creatinine > 2 mg/dL or > 177 µmol/L, as detected in at least two lab values on two different days within a period extending between day -24 and the start of the systemic therapy regimen. If no systemic therapy was given, then it would be day -24 and the cellular therapy infusion date. If only a single value was reported in this time period, use the most recent test performed between days -40 & -25 as the second value.

Report “yes” to question 253 if the recipient has a documented history and/or current diagnosis of any of the following:

Documented Medical History	Question Number
Arrythmia	254
Cardiac[2]	255
Cerebrovascular disease	256
Heart valve disease[3]	258
Inflammatory bowel disease	262
Peptic ulcer	264

Current Diagnosis at the Time of Pre-HCT Evaluation	Question Number
Rheumatologic	269

Solid tumor, prior[4]	270
Diabetes	257
Hepatic, mild[5]	259
Hepatic, moderate/severe	260
Infection	261
Obesity	263
Psychiatric disturbance	265
Pulmonary, moderate	266
Pulmonary, severe	267
Renal, moderate/severe[6]	268
Other (specify)	289 and 290

[2] Ejection fraction (EF) ≤ 50% should be reported only if present on most recent test

[3] Excluding asymptomatic mitral valve prolapse

[4] Excluding non-melanoma skin cancer, leukemia, lymphoma, or multiple myeloma

[5] Including any history of hepatitis B or hepatitis C infection

[6] Including renal transplantation at any time in the patient's history

The intent of this question is to identify serious pre-existing conditions that may have an effect on the outcome of the cellular therapy. For the purposes of this manual, the term "clinically significant" refers to conditions that are being treated at the time of pre-infusion evaluation, or are in the recipient's medical history and could cause complications post-infusion. Conditions listed in the recipient's medical history that have been resolved (e.g., appendectomy), and/or that would not pose a concern during or after the infusion should not be reported.

Additionally, for the purposes of this manual, the term "at the time of patient assessment" is defined as the pre-infusion evaluation period prior to the start of the preparative regimen. If the recipient does not have a documented history of clinically significant disease(s) or organ impairment(s), check "no" and continue with question 291.

For information regarding reporting clinically significant co-existing disease or organ impairment, see Appendix J.

Questions 254-290: Co-existing diseases or organ impairments

For each listed co-existing disease or organ impairment, check “yes,” “no,” or “unknown.”

Arrhythmia: Any history of atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring treatment.

Cardiac: Any history of coronary artery disease (one or more vessel coronary artery stenosis requiring medical treatment, stent, or bypass graft), congestive heart failure, myocardial infarction, or ejection fraction < 50% on the most recent test.

Cerebrovascular disease: Any history of transient ischemic attack, subarachnoid hemorrhage, or cerebrovascular accident.

Diabetes: Requiring treatment with insulin or oral hypoglycemics in the last 4 weeks but not diet alone

Heart valve disease: Except asymptomatic mitral prolapse.

Hepatic (mild): Chronic hepatitis, bilirubin > upper limit of normal to 1.5x upper limit of normal, or AST/ALT > upper limit of normal to 2.5x upper limit of normal, or any history of hepatitis B or hepatitis C infection. *See note in question 97.*

Hepatic (moderate/severe): Liver cirrhosis, bilirubin > 1.5x upper limit of normal, or AST/ALT > 2.5x upper limit of normal. *See note in question 97.*

Infection: Documented infection, fever of unknown origin, or pulmonary nodules requiring continuation of antimicrobial treatment after day 0.

Inflammatory bowel disease: Any history of Crohn’s disease or ulcerative colitis requiring treatment.

Obesity: Patients with a body mass index > 35 kg/m^2 or BMI-for-age ≥ 95% (pediatric recipients only) during pre-transplant work-up period.

Peptic ulcer: Any history of peptic ulcer confirmed by endoscopy and requiring treatment.

Psychiatric disturbance: Depression, anxiety, bipolar disorder, or schizophrenia requiring psychiatric consult or treatment in the last 4 weeks.

Pulmonary (moderate): Corrected diffusion capacity of carbon monoxide (e.g., DLCOc, DLCOcorr, DLCO) and/or FEV1 66-80% or dyspnea on slight activity at transplant.

Pulmonary (severe): Corrected diffusion capacity of carbon monoxide (e.g., DLCOc, DLCOcorr, DLCO) and/or FEV1 ≤ 65% or dyspnea at rest or requiring oxygen at transplant.

Renal (moderate/severe): Serum creatinine > 2 mg/dL or > 177 µmol/L, or on dialysis at transplant, or prior renal transplantation. *See note in question 97.*

Rheumatologic: Any history of systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, or polymyalgia rheumatica requiring treatment (do NOT include degenerative joint disease, osteoarthritis)

Solid tumor (prior): Treated at any time point in the patient's past history, excluding non-melanoma skin cancer, leukemia, lymphoma, or multiple myeloma. For each listed prior solid tumor, check "yes" or "no." If "yes," enter the year of diagnosis of the corresponding solid tumor.

Other co-morbid condition: The "other, specify" category should be used to report co-morbid conditions that are of similar clinical concern as the other listed options. Chromosomal abnormalities, impairments and/or disorders associated with the primary disease should not be reported in this section, (e.g., Ph+ for CML/ALL recipients).

Question 291: Was there a history of malignancy (hematologic or non-melanoma skin cancer) other than the primary disease for which this cellular therapy is being performed?

The intent of this question is to identify other malignancies that may have an effect on the outcome of the cellular therapy. A history of any benign tumor(s) should not be reported in this section. Malignancies reported in the previous solid tumor options should not be reported again here.
If the recipient receives an infusion for a disease that has transformed from one disease to another, the original malignancy should not be reported in this section. Details regarding disease transformation will be captured on the Disease Classification form (Form 2402). For more information regarding disease combinations and transformations, refer to the Common Disease Combinations and Common Disease Transformations tables in the Primary Disease for HCT / Cellular Therapy section of the Disease Classification Form (Form 2402).

Indicate if there was a history of hematologic malignancy or non-melanoma skin cancer other than the disease for which this infusion is being performed.

Question 292-311: Specify which malignancy(ies) occurred:

For each listed prior malignancy, check "yes" or "no." If "yes," enter the year of diagnosis of the corresponding malignancy.
Use questions 292-311 to report any prior hematologic malignancies or non-melanoma skin cancer that were not listed in questions 254-290. Solid tumors (except for non-melanoma skin cancers) should be

reported in questions 270-288, not in questions 309-311.

[1] Sorror, M. L. (2013). How I assess comorbidities before hematopoietic cell transplantation. Blood, 121(15), 2854-2863.

Last modified: 2019/06/27

4003: Cellular Therapy Product

This form must be completed for all products for recipients of non-HCT cellular therapy (including post-HCT "DCI/DLI" infusions). For recipients of hematopoietic cellular transplants (HCT), complete the appropriate HCT infusion form (Form 2006).

The Form 4003 is designed to capture product specific information for all products/infusions given to a recipient as part of a course of cellular therapy. In addition to use in research, this information is used for quality assurance measures, both by the NMDP and the Cord Blood Banks.

A series of collections from the same donor that uses the same collection method and mobilization cycle, even if the collections are performed on different days, should be considered a single cellular therapy product if only one set of manufacturing steps are applied to the collected material.

If more than one type of cellular therapy product is infused, each product type must be analyzed and reported on a separate form 4003. Products from the same donor but obtained using different manufacturing steps are considered different products and require multiple 4003 forms, one for each product.

Additionally, if the cells were manipulated or modified by different methods and at the end of the manufacturing process are combined for a single infusion or administration, it will be considered a single product and it will require a single Form 4003.

For more information see Appendix D–How to Distinguish Infusion Types and Appendix E–Definition of a Product.

Links to sections of form:

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.
If you need to reference the historical Manual Change History for this form, please click here or reference the retired manual section on the Retired Forms Manuals.

Date	Manual Section	Add/ Remove/ Modify	Description
6/ 27/ 19	4003: Cellular Therapy Product	Modify	Added additional information to the manual providing specific reporting instructions for commercially available products.
1/ 25/ 19	4003: Cellular Therapy Product	Modify	Version 2 of the 4003: Cell Therapy Product section of the Forms Instruction Manual released. Version 2 corresponds to revision 2 of the Form 4003.

Last modified: 2019/06/27

Q1-19: Cellular Therapy Product Identification

If more than one cell therapy product is infused, each product must be reported on a separate 4003 form.

Question 1: Name of product:

The name of the product reported here must match what was reported on Form 4000 question 42. This question is limited to commercialized products and is used to disable questions related to manufacturing. If the name of the product is not an option or if the product has no commercialized name (e.g. DCI/DLI product), select 'other product' from the list.

If a commercially available product is selected, several questions on this form will be disabled and cannot be answered.

Question 2: Specify donor:

Indicate the donor type for this product. If the product is "off the shelf" or a "third party" donor product obtained from pharmaceutical companies or other corporate entities, donor type should still be identified.

An autologous product has cells collected from the recipient for his/her own use. Continue with question 4.

A related donor (allogeneic, related) is a blood-related relative. This includes syngeneic, monozygotic (identical) twins, non-monozygotic (dizygotic, fraternal, non-identical) twins, siblings, parents, aunts, uncles, children, cousins, half-siblings, etc. Do not include adoptive parents/children or stepparents/children. Continue with question 4.

An unrelated donor (allogeneic, unrelated) is a donor who shares no known ancestry with the recipient. Include adoptive parents/children or stepparents/children.
Continue with question 3.

Question 3: Did NMDP/Be the Match facilitate the procurement, collection, or transportation of the product?

Distinguish if the product is an NMDP product or a non-NMDP product. Examples of non-NMDP donor registries include, but are not limited to: St. Louis Cord Blood Bank, Anthony Nolan, and StemCyte International Cord Blood Center. This information is included on the product label, the paperwork accompanying the product, and within the NMDP search/product documentation.

Question 4: Was the product a cord blood unit?

Indicate “yes” if the product was a cord blood unit.

- If the product was an **autologous** cord blood unit, continue with question 8 to report the non-NMDP CBU ID.
- If the product was a **related** cord blood unit, continue with question 8 to report the non-NMDP CBU ID.
- If the product was an **NMDP unrelated** cord blood unit, continue with question 5 to report the NMDP CBU ID.
- If the product was a **non-NMDP unrelated** cord blood unit, continue with question 8 to report the non-NMDP CBU ID.

Indicate “no” if the product was not a cord blood unit.

- If the **autologous** product was not a CBU, continue with question 19.
- If the product was **related** but not a CBU, continue with question 14 to report donor DOB.
- If the unrelated donor was **NMDP** but not a CBU, report the NMDP donor ID in question 6
- If the unrelated donor was **non-NMDP** but not a CBU, report the non-NMDP unrelated donor ID in question 7

Question 5: NMDP Cord Blood Unit:

Report the NMDP Cord Blood Unit ID. This information is included on the product label, the product insert accompanying the product, and within the NMDP search/product documentation. The ID is always numeric and begins with “9” (e.g., 9000-0000-0). If the product ID does not begin with a “9,” the product may not be an NMDP cord blood unit and the source of the product should be double-checked. Continue with question 19.

Question 6: NMDP Donor ID:

Report the NMDP Donor ID. This information is included on the product label, the product insert accompanying the product, and within the NMDP search/product documentation. The ID is always numeric (e.g., 0000-0000-0) and is unique for each donor, assigned by the NMDP. Continue with question 19.

Question 7: Non-NMDP unrelated donor ID: (not applicable for related donors)

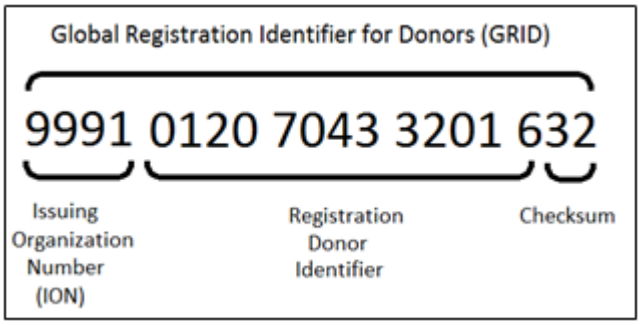
Do not complete this field if the recipient has an NMDP donor, a related donor, or a cord blood donor. This ID is often located on the product label, the product insert accompanying the product, and the registry-specific search/product documentation. Continue with question 9.

Question 8: Non-NMDP cord blood unit ID: (include related and autologous CBUs)

Examples of non-NMDP donor registries include, but are not limited to: St. Louis Cord Blood Bank and StemCyte International Cord Blood Center. This ID is often located on the product label, the paperwork accompanying the product, and registry specific search/product documentation. Enter the non-NMDP cord blood ID. Note that some cord blood banks can ship their units either through the NMDP or directly to the center. Carefully review the accompanying documentation to determine which is appropriate for your unit. You may wish to consult with your center's Transplant Coordinator, as they will have insight as to how the product was acquired. Continue with question 9.

Question 9: Global Registration Identifier for Donors (GRID):

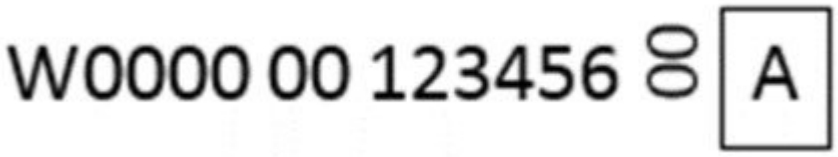
The Global Registration Identifier for Donors (GRID) was developed by the WMDA to ensure secure, reliable and unambiguous assignment of donors. The GRID standard is a 19-character donor identifier composed of three elements: Issuing Organization Number (ION), Registration Donor Identifier, and Checksum (shown below). This standard will ensure each donor ID is globally unique and will reduce the risk of misidentification of donors or their donations.



https://www.wmda.info/professionals/optimising-search-match-connect/why-global-identifier/

Question 10: Is there an ISBT DIN number associated with the product?

Report "yes" if there is an International Society of Blood Transfusion (ISBT) Donation Identification Number (DIN) associated with the product. If the product is a cord blood unit, continue with question 11, all other products continue with question 13. If the product has an ISBT label on it, the ISBT DIN number is in the upper left-hand corner and consists of a letter followed by 12 numbers, two numbers on the end, and a letter in a box. Example below:



Please find additional information regarding the ISBT DIN numbers and traceability at ISBT 128 Basics. For example, you may see a barcode with an alphanumeric string below it.

Report “no” if there isn’t an ISBT DIN associated with the product. If the donor is auto, continue with question 20. If the donor is related continue with question 15. If the donor is unrelated, non-NMDP continue with question 13.

Question 11: Is the CBU ID also the ISBT DIN number?

Answered only for cord blood units. Report “yes” if the non-NMDP CBU ID is the same as the International Society of Blood Transfusion (ISBT) Donation Identification Number (DIN) and continue with question 13.

If the CBU ID is not the same as the ISBT DIN number, select “no” and continue with question 12.

Question 12: Specify the ISBT DIN number:

Report the ISBT DIN number using the letter, 12 digits, 2 numbers on end, and the letter in the box. See question 10 for an explanation on ISBT DIN.

Question 13-14: Registry or UCB Bank ID:

Specify the registry used to obtain the adult donor or umbilical cord blood unit. The Bone Marrow Donors Worldwide codes have been adopted to avoid submitting the entire name and address of the donor registry.

For example, the registry code for Belgium donors is (B) but Belgium cord blood units the registry code is (BCB).

Some common banks that do not list with BMDW have been added to the Form 2006 revision 4 list, including St Louis Cord Blood Bank (SLCBB) and Viacord (VIAC).

If the donor was found through DKMS, report the registry that facilitated the cellular therapy product. Some registries may be listed more than once with BMDW (once for marrow/PBSC products and differently for cord blood products). Ensure that the appropriate code for the product was selected, because distribution of data is dependent on the code.

If there is no match code for the adult donor registry or cord blood bank, provide the registry's official name in the "Specify other registry" field.

Please ensure that the registry you are entering under "other" is not already listed in the pull-down list for question 13. Entries such as NMDP adult donors, NMDP cords, and New York Cord Bank each have their own entries above.

Question 15-16: Date of birth (donor / infant):

For related or non-NMDP donors only, report if the donor's/infant's date of birth is "known" or "unknown" for question 15. If the donor's/infant's date of birth is known, report the date of birth (YYYY-MM-DD) in question 16. If the donor's/infant's date of birth is unknown, continue with question 17.

Question 17-18: Age (donor / infant):

For related or non-NMDP donors only, if the DOB is unknown, report if the donor's/infant's age is "known" or "unknown" for question 17. If the donor's/infant's age is known, report the donor's/infant's age at the time of product collection in question 18. Report the age in months if the recipient is less than 1 year old, otherwise report the age in years. If the donor's/infant's age at collection is unknown, continue with question 19.

Question 19: Sex (donor / infant):

For related or NMDP donors only, indicate the donor's biological sex as "male" or "female." For cord blood units, report the infant donor's sex.

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Q20-21: Cell Product Source

Question 20-21: Date of cell product collection

Report if the date of cell product collection is “known” or “unknown” for question 20. If the date of cell product collection is known, report the date (YYYY-MM-DD) in question 21. If the date of cell product collection is unknown, continue with question 22.

If the exact date is not known, General Instructions, General Guidelines for Completing Forms for more information regarding reporting partial or unknown dates.

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Q22-27: Collection Procedure

This section applies to Autologous infusions only. If this was an allogeneic infusion, continue to question 28.

Question 22: Did the recipient have more than one mobilization event to acquire cells?

This question applies only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 24.

Stem cells do not typically circulate in the bloodstream. Therefore, in order to increase the quantity of cells for collection, an agent is frequently given to the autologous recipient. The purpose of the agent is to move the stem cells from the bone marrow into the peripheral blood. This practice is often referred to as mobilization or priming. Occasionally, a bone marrow product may be primed using a growth factor.

For the purposes of this manual, the CIBMTR defines a mobilization event as the planned administration of growth factors or systemic therapy designed to enhance stem cell collection. If the donor requires an additional mobilization at a later date to collect an additional product, this should be considered an additional mobilization event. If the mobilization methods change (e.g., plerixafor is added starting on Day 3 of collection) this would be considered an additional mobilization event.

Example 1: An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection. Since the collection and mobilization methods remained the same over the duration of the collection, this is considered one mobilization event.

Example 2: An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection, but the cell count was poor. GM-CSF was administered and the autologous recipient was re-collected. This is considered two mobilization events due to the change in mobilization drugs administered.

Example 3: An autologous recipient was mobilized with G-CSF and underwent a one-day PBSC collection, but the cell count was poor. The recipient then received plerixafor to enhance the mobilization. This is considered two mobilization events due to the change in mobilization drugs administered.

If more than one mobilization event occurred, report the number of events in question 23, else continue with question 24.

Question 23: Specify the total number of mobilization events performed for this cellular therapy: (regardless of the number of collections or which collections were used)

> ✻ This question applies only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 24.

Report the total number of mobilization events performed for this cellular therapy. Include all mobilization events, even if a product from the mobilization event for this cellular therapy was not used during the infusion. See examples in question 24 for more details.

Question 24: Number of collections:

Report the number of collections that occurred after the mobilization event(s) reported in questions 22 and 23. It is possible to have more than one collection per mobilization or a failed mobilization with no collection.

Example 1: (from above) An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection. The mobilization methods remained the same but the number of collections reported will be two.

Example 2: (from above) An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection, but the cell count was poor. GM-CSF was administered and the autologous recipient underwent another collection. This is considered two mobilization events, but three collections.

Question 25-26: Specify the method of product collection:

Specify how the product was collected:

Bone marrow aspirate: a small sample of liquid bone marrow is removed, usually from the hip bone, breastbone, or thigh bone.
Leukapheresis: removal of blood to collect specific blood cells
Byoptic sample: sample taken from a biopsy, typically a tumor biopsy.
Other method: not fitting in a category listed above.

If the method of product collection is selected as ‘Other method’, specify the other product collection method in question 26 and continue with question 27.

Question 27: Specify agent(s) used in the mobilization events: (check all that apply)

> This question applies only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 28.

Report if any of the following agents were used in the mobilization event(s) reported in questions 22-23.

G-CSF: granulocyte colony-stimulating factor, filgrastim, Neupogen®
GM-CSF: granulocyte macrophage colony-stimulating factor, sargramostim, Leukine®
Peglygated G-CSF: pegfilgrastim, Neulasta
Plerixafor: Mozobil
Other CXCR4 inhibitor: examples include POL6326 and AMD3465. Report experimental and other CXCR4 inhibitors used to mobilize the donor here.

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Q28-59: Cell Product Manipulation

This section applies only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 60.

This section specifies any manipulation that was done to manufacture the final cellular therapy product.

Question 28: Were the cells in the infused product selected / modified / engineered prior to infusion?

Indicate “yes” if the cells contained in the product were selected (i.e. selective retention of a population of desired cells through recognition of specified characteristics), modified or genetically engineered and continue with question 29. Indicate “no” if the cells contained in the product were not selected, modified or genetically engineered in any way prior to infusion and continue with question 53.

Question 29: Specify the portion manipulated:

If the product being infused as a cellular therapy (e.g. DLI/DCI) is a portion from a prior HCT, the portion becomes the “entire” product for the purposes of this form. The product can then be further divided.

Indicate the portion of the product that was manipulated. If the entire product was manipulated, select “entire product” and continue with question 31.

If a portion of the product was removed and manipulated, select “portion of product” and continue with question 30.

Question 30: Was the unmanipulated portion of the product also infused?

Indicate “yes” if the unmanipulated portion of the product was also infused. Indicate “no” if the unmanipulated portion of the product was not infused.

Question 31: Was the same manipulation method used on the entire product / all portions of the product?

If the same manipulation was used on the entire product or all portions of the product, indicate “yes”. If different manipulation methods were used indicate “no”. All manipulations for each portion of the product should be reported in questions 32-59.

Question 32-33: Specify method(s) used to manipulate the product: (check all that apply)

Indicate the method(s) of manipulation.

Steps in Manipulation
If the manipulation consists of several steps, individual steps do not need to be reported as separate manipulations. For example, T-cell depletion that is part of expansion does not need to be reported. However, if T-cell depletion and/or washing are done as standalone manipulations, they should be reported.

Cryopreservation as a Manipulation
Do not report cryopreservation (including plasma removal as part of cryopreservation) as a method of manipulation

Cultured (ex-vivo expansion): cells were placed in culture to increase in number (i.e. to expand) allowing for sufficient cells for infusion. Continue with question 53.

Induced cell differentiation: cells were placed in culture to give rise to cellular elements with biological characteristics other than those of the cells being cultured (i.e. mesenchymal stromal cells cultured to make osteoblasts; pluripotent stem cells cultured to make neural cell precursors). Usually, the description of the process would include the term “differentiation of cells X into cells Y”. This scenario can be seen in regenerative medicine indications. Continue with question 53.

Cell selection – positive: the manipulation of a cellular therapy product that a specific cell population(s) is enriched. This may be achieved by using an antibody that binds to a specific population of cells (e.g., CD3+ selection). Continue with question 53.

Cell selection – negative: the manipulation of a cellular therapy product such that a specific cell population(s) is reduced. Continue with question 53.

Cell selection based on affinity to a specific antigen: the cellular product undergoes selection to isolate the target population based on the ability of the target population to bind or recognize a specific antigen (e.g. a T cell population recognizing viral proteins or a protein associated with a cancer).
Continue with question 53.

Genetic manipulation (gene transfer / transduction): cells are manipulated via gene transfer, a process by which copies of a gene are inserted into living cells in order to induce synthesis of the gene’s product; or transduction, a process by which foreign DNA is introduced into a cell by a virus or viral vector. These

techniques deliberately alter the genetic material of an organism in order to make them capable of making new substances or performing new or different functions. Continue with question 34 to report the types of genetic manipulation.

Other cell manipulation: not fitting an above category. Specify manipulation in question 32 and continue with question 53.

Questions 34-52: Specify the type of genetic manipulation.
This section only applies if “genetic manipulation” was selected in question 31

Question 34-42: Transfection:

Transfection is a process of deliberately introducing naked or purified nucleic acids by viral or non-viral methods into eukaryotic cells. Continue with question 35 if the product underwent transfection or continue with question 43 if it did not.

Viral transduction: Viral transduction occurs when there is gene transfer by infection of a cell with nucleic acid by a virus, followed by viral replication in the affected cell. If “yes”, indicate the virus used in the viral transduction in questions 36 and 37. Indicate “no” if the product did not undergo viral transduction and continue with question 38.

Lentivirus: 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. Indicate “no” if a Lentivirus was not used for the viral transfection.

Retrovirus: 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. Indicate “no” if a Retrovirus was not used for the viral transfection.

Non-Viral transfection: Non-viral transfection is the process of deliberately introducing naked or purified nucleic acids into eukaryotic cells. If “yes”, indicate the method of non-viral transfection in question 39-42. Indicate “no” if the product did not undergo non-viral transfection and continue with question 43.

Transposon: Transposons are discrete mobile sequences in the genome that can transport themselves directly from one part of the genome to another without the use of a vehicle such as phage or plasmid DNA. They are able to move by making DNA copies of their RNA transcripts which are then incorporated into the genome at a new site. Indicate “no” if Transposons were not used for the non-viral transfection.

Electroporation: Electroporation is a process of introducing DNA or chromosomes into cells using a pulse of

electricity to briefly open the pores in the cell membranes. Indicate “no” if Electroporation was not used for the non-viral transfection.

Other non-viral transfection: Indicate “yes” if a different non-viral transfection method not previously listed was utilized. Specify the other non-viral transfection method in question 42.

Question 43-45: Gene editing:

Gene editing is a type of genetic engineering in which DNA is inserted or removed from a genome using artificially engineered nucleases. If “yes”, specify which gene was edited in the manipulation in question 57.

If “other gene” is answered for question 44, specify the gene in question 45. Indicate “no” for question 43 if the cells did not undergo gene editing.

Question 46: Were cells engineered to express a non-native antigen receptor?

Indicate “yes” if the cells underwent a type of genetic engineering in which a gene is transferred codes for an antigen receptor other than one that may already be naturally present in the cell (e.g. T-cells have natural T-cell receptors [TCRs]; a transgenic TCR or a Chimeric Antigen Receptor [CAR] are non- native antigen receptors). Indicate “no” if the cells did not undergo transfer of such a gene and continue with question 63.

Question 47-50: Specify the protein inserted into the cellular product:

Specify which construct was utilized as part of the genetic manipulation process:

T-cell receptor: Heterodimeric antigen receptors present on the surface of T-cells1. Continue with question 51.

Chimeric Antigen Receptor (CAR): A cell-surface receptor that has been engineered to combine novel features and specificities from various sources in order to enhance its antigen specificity. Engineered T-cells or B-cells will produce the specialized receptor that will be capable of binding to an epitope on its target cell[1].

The CAR construct consists of several genes that can exert different functions, such as augment the immune response by co-stimulation, increase affinity, and increase the time it persists in the circulation without being cleared. The CAR construct information is usually unique and may influence its effect against the disease or the severity of side effects. Specify which construct(s) was used in the making of the Chimeric Antigen Receptor (CAR) in question 47. If a construct was utilized that is not in the list, check “other construct” and specify in question 49.

For more information related to the different constructs and their functions, see this article: https://www.jci.org/articles/view/80010.

Suicide gene: cells underwent manipulation to have cell suicide inducing transgenes inserted into the product. Specify the suicide gene in question 50.

Question 51-52: Other genetic manipulation:

Indicate “yes” for other genetic manipulation that does not fit into a category listed above and specify in question 52.

Question 53-54: Was the product manipulated to recognize a specific target/antigen?

Indicate “yes” if the cells were cultured or engineered so that the majority of cells in the end product are able to recognize or bind to a chosen target (e.g. proteins from a virus or a protein from a tumor) and specify the target in question 54. This manipulation can be done outside of the context of ‘genetic manipulation’. If “no”, continue with question 60.

If the target is viral, continue with question 55.

If the target is tumor/cancer antigen, continue with question 57.

If the target is something other than viral or tumor/cancer antigen, continue with question 59.

Question 55-56: Specify viral target(s): (check all that apply):

Select all viral target(s) that apply to the product. If the target is “other virus”, specify in question 56. Continue with question 60.

Question 57-58: Specify the target antigen:

Select all target antigen(s) that apply to the product. If the target is “other target antigen”, specify in question 58. Continue with question 60.

Question 59: Specify other target:

If the product was manipulated to recognize a specific target/antigen that does fit in a category above, specify the other target. Continue with question 60.

[1] NCIthesarus: https://ncit.nci.nih.gov/ncitbrowser/

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Q60-68: Cell Product Analysis

Questions 60-63 apply only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 69.

Question 60: Was transfection efficiency done? (genetically engineered cells)

Answered for genetically engineered cells only. Transfection efficiency is calculated as a percentage of transfected cells from all cells in the sample. There are a number of methods used to determine transfection efficiency including flow cytometry, fluorometry, microscopy, real-time quantitative PCR, etc.

Question 61: Date:

Specify the date (YYYY-MM-DD) when sample was taken for the transfection efficiency testing.

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 62: Transfection efficiency:

Report the percent transfection efficiency. Round to the nearest whole number.

Question 63: Was transfection efficiency target achieved?

Transfection efficiency target will be defined by the protocol. Indicate “yes” or “no” if the target defined by the protocol was met.

Questions 64-68 apply only to products that are not commercially available. If a commercially available product (Kymriah® or Yescarta®) was selected in question one, continue to question 69.

Question 64: Was viability of cells done?

If the viability of the cells was quantified, select “yes” and report the date the sample was collected to determine viability in question 65 and the percentage of viable cells in question 66. Methods of testing cell viability are listed in question 67.

Question 65: Date:

Specify the date (YYYY-MM-DD) when the sample was collected to determine viability.

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 66: Viability of cells:

Report the percent viability. Round to the nearest whole number.

Question 67-68: Method of testing cell viability:

Indicate the method of testing viability.

7-AAD (7-aminoactinomycinD) and Propidiumiodide are compounds that can stain dead cells but will not cross the membrane of living cells. Cytometric techniques are used to calculate the percentage of viable cells in a sample.

Trypan Blue is a technique where the dead cells become stained when in contact with the compound, but living cells remain impermeable to the dye. Cells are counted under a microscope to determine the percentage of viable cells in a sample.

If both methods of viability testing are performed, report 7-AAD results. If the cell viability was tested using a different method, select “other method” and specify the method in question 68.

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Q69: Product Infusion

Question 69: Specify the total number of planned infusions: (of this product) (as part of the course of cellular therapy)

Report the number of infusions specified per protocol. This question is used to make the correct number of Cellular Therapy Infusion forms (Form 4006) come due. Each infusion must be part of the protocol and will be given regardless of disease assessment.

Example 1. The protocol specifies three infusions are to be given as part of the course of cellular therapy. Report the total number of planned infusions as “3”.

Example 2. The protocol specifies five infusions are to be given as part of the course of cellular therapy. The recipient will be assessed after the first three infusions to see if additional infusions will be tolerated (not based on disease status) and two more infusions may be given. Report the total number of planned infusions as “5”. If the last two infusions do not occur, contact your CIBMTR CRC.

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4006: Cellular Therapy Infusion

This form must be completed for all infusions for recipients of non-HCT cellular therapy (including post-HCT "DCI/DLI" infusions). For recipients of hematopoietic cellular transplants (HCT), complete the appropriate HCT infusion form (Form 2006).

The Form 4006 is designed to capture infusion-specific information for all infusions given to a recipient as part of a course of cellular therapy. In addition to use in research, this information is used for quality assurance measures, both by the NMDP and the Cord Blood Banks.

Product specific information is collected on Cellular Therapy Product Form 4003. A Form 4003 is required for each product and a Form 4006 is required for each infusion of that product. For example, a single product may be infused three times per course of cellular therapy.

If more than one infusion occurs, as defined by event date, each infusion must be analyzed and reported on a separate form 4006. This is true even if it's the same product being infused on a later date.

For more information see Appendix D–How to Distinguish Infusion Types and Appendix E–Definition of a Product.

Links to sections of form:
Q1-45: Product Infusion
Q46-49: Concomitant Therapy

Date	Manual Section	Add/ Remove/ Modify	Description
8/29/ 2019	"4006: Product Identification"	Modify	Updated instruction in pink warning box above question 17: **Question 17-45: Reporting total number of cells** Report the total number of cells (not cells per kilogram) contained in the product administered ~~not corrected for viability~~.
6/27/ 19	4006: Cellular Therapy Infusion	Modify	Added additional information to the manual providing specific reporting instructions for commercially available products.
4/10/ 18	4006: Cellular Therapy Infusion	Add	Added in additional clarification regarding total cell counts administered, what constitutes unselected lymphocytes, and T-helper cells (Q17-24).
3/8/ 18	4006: Cellular Therapy	Add	Added **Product Identification** note box above question 1.

	Infusion		
1/30/18	4006: Cellular Therapy Infusion	Modify	Version 3 of the 4006: Cell Therapy Infusion section of the Forms Instructions Manual released. Version 3 corresponds to revision 3 of the Form 4006.

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Q1-45: Product Identification

Questions 1-6: Not all of these identifiers are applicable to all products. The ID / number should be found with the product bag or shipping manifest. Choose the identifier that is most appropriate. Please do not override a field, but rather select yes or no.

Question 1-2: Cell product ID :

If the cellular therapy product infused is the commercially available product Kymriah® or Yescarta®, report the cell product ID as “no”.

Report if the product has a Cell product ID in question 1 and specify the ID in question 2. Product IDs can be numeric or alphanumeric.

Question 3-4: Batch number:

If the cellular therapy product infused is the commercially available product Kymriah®, the batch number must be reported and is available with the information that comes with the product.

If the cellular therapy product infused is the commercially available product Yescarta®, report the batch number as “no”.

Report if the product has a Batch number in question 3 and specify the Batch number in question 4. Batch numbers can be numeric or alphanumeric

Question 5-6: Lot number:

If the cellular therapy product infused is the commercially available product Kymriah®, report the lot number as “no”.

If the cellular therapy product infused is the commercially available product Yescarta®, the

> lot number must be reported and is available with the information that comes with the product.

Report if the product has a Lot number in question 5 and specify the Lot number in question 6. Lot numbers can be numeric or alphanumeric

Question 7: Date of this product infusion:

Report the date (YYYY-MM-DD) this product was infused. If the product was infused over multiple days, report the first date of infusion.

If the exact date is unknown, please view General Instructions, General Guidelines for Completing Forms for more information on reporting partial and unknown dates.

Question 8-10: Was the entire volume of product infused?

If the product being infused as a cellular therapy (e.g. DLI/DCI) is a portion from a prior HCT, the portion becomes the “entire” product for the purposes of this form. The intent is to capture if the product being infused was given in its entirety or not.

If the entire volume of the product was not infused, specify what happened to the reserved portion in question 9 and 10.

Question 11-12: Specify the route of product infusion:

> ✻ If the cellular therapy product infused is the commercially available product Kymriah® or Yescarta®, report the route of infusion as “intravenous”.

Report the route by which the product was infused.

Intravenous refers to an infusion into the veins – examples include infusion via central line or via catheter.
Intramedullary refers to an infusion into the marrow cavity within a bone, such as directly into the proximal tibia or anterior aspect of the femur.
Intraperitoneal refers to an infusion within the peritoneal cavity.
Intra-arterial refers to an infusion within an artery or arteries.
Intramuscular refers to an infusion within a muscle.
Intrathecal refers to an infusion within the cerebrospinal fluid at any level of the cerebrospinal axis, including injection into the cerebral ventricles.

Intraorgan refers to an infusion within an organ such as the heart, liver, lungs, etc. Specify the site in question 13.
Locally in the tissue refers to an infusion in a restricted area of the body or in a tumor that cannot be classified as intraorgan.

If the route of infusion is not one of the above options, select “other route of infusion” and specify the infusion route in question 12.

Question 13-14: Specify the site of intraorgan administration of cells:

If the route of product infusion was intraorgan, specify the site of intraorgan administration. If the site of infusion is not in the option list, select “other site” and specify the site in question 14.

Question 15: Recipient weight used for this infusion:

Report the recipient’s actual body weight used to calculate the cell dose for this infusion. This weight is usually documented on infusion orders or admitting orders. Report weight to the nearest whole kilogram or pound (round up if 0.5 or greater). Do not report adjusted body weight, lean body weight, or ideal body weight.

Question 16: Recipient height used for this infusion:

Report the recipient’s height at infusion. Report the recipient’s height to the nearest whole centimeter or inch (round up if 0.5 or greater).

> **Question 17-45: Reporting total number of cells**
> Report the total number of cells (not cells per kilogram) contained in the product administered.

This section collects the total number of cells that were infused in a specific product. All of the cells that were listed on the F4000 Pre-CTED in question 36 are included here. Only respond to the cells that are applicable to *this* infusion. Note, CD3 is present on all T-cells whether they are CD4+ or CD8+ T-cells.

> Cell counts are not released for the commercially available product Yescarta®. Report “unknown” or “no” for all cell types listed in questions 17-45.

Question 17-18: Total number of cells administered:

Report the total cell count contained in the product administered, not corrected for viability. If the type of

cells are not specified, report the total number of cells present at time of the infusion. If multiple bags were infused together, report the sum of each bag.

Question 19-20: Lymphocytes (unselected) administered:

Unselected means a specific lymphocyte sub-population (e.g. CD4+) was not targeted. This includes all types of lymphocytes, those that have not been selected via flow cytometry or other method. If yes, report the total number of unselected lymphocytes (e.g., CD3+ cells) administered in the product in question 20.

Question 21-22: CD4+ lymphocytes administered:

The lab report may display this value as CD3+CD4+. These cells are also known as T-helper cells. If yes, report the total number of CD4+ cells administered in the product in question 22.

Question 23-24: CD8+ lymphocytes administered:

The lab report may display this value as CD3+CD8+. These cells are also known as T-helper cells. If yes, report the total number of CD8+ cells administered in the product in question 24.

Question 25-26: Natural killer cells (NK cells) administered:

NK cells are a type of cytotoxic lymphocyte critical to the innate immune system. They usually express CD56 / CD16 on their cell surface. If yes, report the total number of natural killer cells (NK cells) administered in the product in question 26.

Question 27-28: Dendritic cells / tumor cell hybridomas administered:

Dendritic cells are antigen-presenting cells (also known as accessory cells) of the immune system. Their main function is to process antigen material and present it on the cell surface to the T-cells of the immune system. If yes, report the total number of dendritic cells or tumor cell hybridomas administered in the product in question 28.

Question 29-30: Mesenchymal stromal stem cells (MSCs) administered:

MSCs are multipotent stromal cells that can differentiate into a variety of cell types, including: osteoblasts (bone cells), chondrocytes (cartilage cells), myocytes (muscle cells) and adipocytes (fat cells). If yes, report the total number of MSCs administered in the product in question 30.

Question 31-32: Unspecified mononuclear cells administered:

A mononuclear cell is defined as any blood cell with a round nucleus (i.e., a lymphocyte, a monocyte, or a macrophage). These blood cells are a critical component of the immune system’s ability to fight infection

and adapt to intruders. If yes, report the total number of unspecified mononuclear cells administered in the product in question 32.

Question 33-34: Endothelial progenitor cells (EPC) administered:

EPC is a term that is applied to multiple different cell types that play roles in the regeneration of the endothelial lining of blood vessels. If yes, report the total number of endothelial progenitor cells (EPCs) in the product in question 34.

Question 35-36: Human umbilical cord perivascular (HUCPV) cells administered:

HUCPV cell is a term that is applied to mesenchymal, non-hematopoietic, non-endothelial cells that are isolated from the umbilical cord. If yes, report the total number of human umbilical cord perivascular (HUCPV) cells in the product in question 36

Question 37-38: Cardiac progenitor cells administered:

Cardiac progenitor cells are tissue-specific stem progenitor cells within the heart. If yes, report the total number of cardiac progenitor cells administered in the product in question 38.

Question 39-40: Islet cells administered:

Islet cells are found in the pancreas. The pancreas contains clusters of cells that produce hormones and these clusters are known as islets. If yes, report the total number of islet cells administered in the product in question 40.

Question 41-42: Oligodendrocytes administered:

Oligodendrocytes are glial cells similar to an astrocyte but with fewer protuberances. These cells produce myelin in the central nervous system. If yes, report the total number of oligodendrocytes administered in the product in question 42.

Question 43–45: Other cell type administered:

If a different cell type not previously mentioned was infused, specify the other cell type in question 44 and report the total number administered in the infusion in question 45.

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Q46-49: Concomitant Therapy

Question 46: Did the recipient receive concomitant therapy?

Concomitant therapy is therapy given to enhance the function of the cellular therapy. In cases where a recipient has both HCT and cell therapy, this question applies to the cell therapy infusion, not the HCT. If the recipient had a prior HCT and the therapy was already captured on the HCT form as being HCT prep regimen, it is not reported again. See question 47 for a list of drugs that can be given as concomitant therapy.

Question 47-48: Specify drugs: (check all that apply)

Select the drug(s) given as concomitant therapy. If the drug given is not in the list, check “other” and specify the other drug in question 48.

Question 49: Specify time point:

This question applies to the therapy as a whole, not to each individual drug. Concomitant therapy can be given simultaneously with the cellular therapy infusion or up to 24 hours after infusion (post cell therapy).

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