

# 4100: Cellular Therapy Essential Data Follow-Up

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The Post-Cellular Therapy Essential Data focuses on key follow up information, including the survival status of the recipient, causes of death if the recipient died in the period since the last report, additional cellular infusions performed for the same indication, response to the cellular therapy, development of second or new malignancies, persistence of the cellular product depending on the product, development and severity of cytokine release syndrome and neurotoxicity, and fertility information.

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## Manual Updates:

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

Date	Manual Section	Add/Remove/Modify	Description
4/19/17	4100: Cellular Therapy Essential Data Follow-Up	Add	Added instructions, in red below, to question 39. <i>Report the date (YYYY-MM-DD) the sample was collected for chimerism studies. If multiple studies were performed in the reporting period, report the most recent testing that documents persistence of cells by chimerism studies. If all the chimerism studies are negative for persistence of cells, then report the most recent test performed in the reporting period.</i>
4/19/17	4100: Cellular Therapy Essential Data	Add	Added instructions, in red below, to question 34. <i>Report the date (YYYY-MM-DD) the sample was collected for flow cytometry testing (immunophenotyping). If multiple studies were performed in the reporting period, report the most recent testing that documents persistence of cells by flow</i>

	Follow-Up		<i>cytometry. If all the flow cytometry tests are negative for persistence of cells, then report the most recent test performed in the reporting period.</i>
4/19/17	4100: Cellular Therapy Essential Data Follow-Up	Add	Added instructions, in red below, to question 29. <i>Report the date (YYYY-MM-DD) the sample was collected for molecular assay. If multiple studies were performed in the reporting period, report the most recent testing that documents persistence of cells by molecular assay. If all the molecular assays are negative for persistence of cells, then report the most recent test performed in the reporting period.</i>
7/29/16	4100: Cellular Therapy Essential Data Follow-Up	Add	Version 1 Released
2/15/17	4100: Cellular Therapy Essential Data Follow-Up	Add	Added note box above question 1: <b>Question 1 Date of Contact</b>
2/15/17	4100: Cellular Therapy Essential Data Follow-Up	Add	Added note box above questions 15: <b>Questions 15-16 Subsequent HCT</b>
2/15/17	4100: Cellular Therapy Essential Data Follow-Up	Add	Added note box above question 22: <b>Questions 22-26 New Malignancy</b>

# Q1-6: Survival

## \* Question 1 Date of Contact

For scenarios where both HCT and CT forms will be submitted at the same time, there are duplicate questions across the F2100 and F4100. To reduce the reporting burden, duplicated questions on the Cell Therapy forms are disabled. This includes Survival Status reported on F4100.

### Question 1: Date of actual contact with the recipient to determine medical status for this follow-up report:

Enter the date of actual contact with recipient to evaluate medical status for this follow-up report.

In general, the date of contact should be reported as close to the 100 day, six month, or annual anniversary to the cellular therapy infusion as possible. Report the date of actual contact with the recipient to evaluate medical status for the reporting period. Preferred evaluations include those from the cellular therapy physician, referring physician, or other physician currently assuming responsibility for the recipient's care. In the absence of contact with a physician, other types of contact may include a documented phone call with the recipient, a laboratory evaluation, or any other documented recipient interaction on the date reported. If there was no contact on the exact time point, choose the date of contact closest to the actual time point. Below, the guidelines show an ideal approximate range for reporting each post-cellular therapy time point:

Form	Time Point	Approximate Range
F4100	100 days	+/- 15 days
F4100	6 months	+/- 30 days
F4100	Yearly	+/- 30 days

Recipients are not always seen within the approximate ranges and some discretion is required when determining the date of contact to report. In that case, report the date closest to the date of contact within reason. The examples below assume that efforts were undertaken to retrieve outside medical records from the primary care provider, but source documentation was not available.

**Example 1.** The 100 day date of contact doesn't fall within the ideal approximate range. The recipient had an infusion on 1/1/13 and is seen regularly until 3/1/13. After that, the recipient was referred home and not seen again until 7/1/13 for a restaging exam and 7/5/13 for a meeting to discuss the results.

What to report:

*100 Day Date of Contact:* 3/1/13 (Since there was no contact closer to the ideal date of 4/11/13, this date is acceptable)

*6 Month Date of Contact:* 7/5/13 (note the latest disease assessment would likely be reported as 7/1/13)

**Example 2.** The 100 day date of contact doesn't fall within the ideal approximate range and the recipient wasn't seen again until 1 year post-HCT. The recipient had an infusion on 1/1/12 and is seen regularly until 3/1/12. After that, the recipient was referred home and not seen again until 1/1/13 for a restaging exam and 1/4/13 for a meeting to discuss the results.

What to report:

*100 Day Date of Contact:* 3/1/13 (Since there was no contact closer to the ideal date of 4/11/13, this date is acceptable)

*6 Month Form:* Indicate the recipient is lost to follow-up in FormsNet

*1 Year Date of Contact:* 1/4/13 (note the latest disease assessment would likely be reported as 1/1/13)

**Additional information:**

- A date of contact should never be used multiple times for the same recipient's forms.
  - For example, 6/1/13 should not be reported for both the 6 month and 1 year. Instead, determine the best possible date of contact for each reporting period; if there is not a suitable date of contact for a reporting period, this may indicate that the recipient was lost to follow-up.
- If the recipient has a disease evaluation just after the ideal date of contact, capturing that data on the form may be beneficial.
  - For example, if the recipient's 90 day restaging exam was delayed until day 115 and the physician had contact with the recipient on day 117, the restaging exams can be reported as the latest disease assessment and day 117 would be the ideal date of contact, even though it is just slightly after the ideal approximate range for the date of contact.

**Date of Contact & Death**

In the case of recipient death, the date of contact is also carefully chosen. If the recipient dies, the date of death should be reported as the date of contact regardless of the time until the ideal date of contact. The date of death should be reported no matter where the death took place (inpatient at the transplant facility, at an outside hospital, in a hospice setting, or within the recipient's home).

**Example 3.** The recipient has died before their six month anniversary. The recipient had an infusion on 1/1/13 and was seen regularly through the first 100 days. They had restaging exams on 4/4/13 and seen on 4/8/13, and then died on 5/13/13 in the hospital emergency room.

What to report:

*100 Day Date of Contact:* 4/8/13 (note the latest disease assessment would likely be reported as 4/4/13)

*6 Month Date of Contact:* 5/13/13 (though the death does not occur within the ideal approximate range for 6 months)

**Example 4.** The recipient has died after their six month anniversary. The recipient had an infusion on 1/1/13 and was seen regularly through the first 100 days. The recipient had restaging exams on 4/22/13 and seen on 4/23/13. Based on findings in the restaging exam, the recipient was admitted for additional treatment. The disease was found to be refractory on a 6/25/13 restaging exam, and the recipient was discharged to hospice on 7/8/13. The hospital was notified via telephone that the recipient died on 7/16/13.

What to report:

*100 Day Date of Contact:* 4/23/13 (note the latest disease assessment would likely be reported as 4/22/13)

*6 Month Date of Contact:* 7/16/13 (note the latest disease assessment would likely be reported as 6/25/13)

For more information regarding reporting partial or unknown dates, see [General Instructions, General Guidelines for Completing Forms.](#)

**Question 2: Specify the recipient's survival status at the date of last contact:**

Indicate the clinical status of the recipient on the date of actual contact for follow-up evaluation.

If the recipient is alive, answers to subsequent questions should reflect the recipient's clinical status from the date of the last report. Continue with question 7.

If the recipient has died, answers to subsequent questions should reflect the recipient's clinical status between the date of the last report and immediately prior to death. Continue with question 3.

**Question 3 & 4: Primary cause of death:**

Cause of death is considered the main disease, complication, or injury that leads to death. Do not report the mode of death (e.g., cardiopulmonary arrest). Only one primary cause of death may be specified, select an option from the dropdown list. Continue with question 5.



**Questions 5 & 6 Reporting more than one contributing cause of death**

These questions are optional.

FormsNet3<sup>SM</sup> application: Complete questions 5 & 6 for each contributing cause of death.  
Paper form submission: Copy questions 5 & 6 for each contributing cause of death.

**Question 5 & 6: Contributing cause of death:**

Report any additional causes of death. All contributing causes of death are important for analysis of cellular therapy outcomes.

Report only one cause of death in each row. If it is necessary to use an “other, specify” field, specify only one “other” cause of death.

## Q7-16: Subsequent Cellular Infusions

! All additional cellular therapy infusions given for the same indication per protocol require a separate infusion form (4006). If a cellular therapy was administered for treatment of a different indication, in response to disease progression/no response, or was administration of a new product, a new Form 4000 (Pre-CTED) must be completed.

### Question 7: Has the recipient received a cellular therapy since the date of last report?

Answer “yes” if the recipient received a cellular therapy since the date of last report and continue with question 8. If the recipient has not received a cellular therapy since the date of last report continue with question 14.

### Question 8: Specify the reason for which cellular therapy was given:

If additional infusions were given for the same indication per protocol, continue with question 9. If the reason for cellular therapy was failure to respond or in response to disease assessment, or for a new indication, report the event date in question 14.

### \* Questions 9-13 Reporting Prior Cellular Therapies

Subsequent infusions within the first 100 days should be reported on the F4000. These questions will not enable for the 100 day report.

FormsNet3<sup>SM</sup> application: Complete questions 9-13 to report all infusions given since the date of last report.

Paper form submission: Copy questions 9-13 and complete for all infusions given since the date of the last report.

### Question 9: Infusion date:

Report the date of the cellular therapy infusion since the date of the last report.

### Question 10: Specify cell source:

Specify the cell source of the cellular therapy reported in question 9.

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.

#### Question 11: Specify the related donor type:

Indicate the relationship and match between the recipient and the donor.

##### **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.

*Does not include:* Half-siblings (report as "HLA matched other relatives" if their HLA 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).

*Does not include:* Adoptive parents/children or stepparents/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 (e.g., parents, aunts, uncles, children, cousins, half-siblings).

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

#### Question 12: Was this donor used for any prior cellular therapies?

Indicate if the allogeneic unrelated or related donor reported in question 10 was used for prior cellular therapies for this recipient. **Do not answer this question for autologous donors.**



### Question 13: Was 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). Answer “yes” if the cellular therapy product the recipient received was genetically modified. Answer “no” if the cellular product was not genetically modified. Continue with question 15.

### Question 14: Event date

Report the date (YYYY-MM-DD) if the reason for cellular therapy was failure to respond or in response to disease assessment, or for a new indication.



#### Questions 15-16 Subsequent HCT

For scenarios where both HCT and CT forms will be submitted at the same time, there are duplicate questions across the F2100 and F4100. To reduce the reporting burden, duplicated questions on the Cell Therapy forms are disabled. This includes subsequent HCT reported on F4100

### Question 15 & 16: Did the recipient receive an HCT since the date of last report?

If the recipient received an HCT since the date of the last report, report the date of HCT in question 16 and also complete CIBMTR HCT form 2400.

If the recipient did not receive an HCT, continue with question 17.

## Q17-19: Best Response to Cellular Therapy

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This section might not fit perfectly to all possible indications of cellular therapy. Please select the response that would most apply to the indication being treated.

### Question 17: What was the best response to the cellular therapy?

This section collects the data known as “best response to cellular therapy”. This section applies to both malignant and non-malignant diseases or disorders. For malignant diseases, appropriate responses would be “complete response”, “partial response”, “no response”, “disease progression” or “unknown”. For non-malignant disorders, appropriate responses would be “normalization of organ function”, “partial normalization of organ function”, “no response”, “worsening of organ function” or “unknown”. If the indication is infection, the appropriate responses would be “complete response”, “partial response”, “no response”, or “unknown”.

If the recipient relapses/progresses and receives therapy for the disease relapse/progression, the response to that additional therapy should not be reported in this section. The best response prior to the relapse/progression should be reported.

### Question 18 & 19: Was the date of best response previously reported?

If the date of best response was previously reported, select “yes” and continue with question 20. **This option is not available on the 100 day report.**

If the date of best response has not been reported, select “no” and report the date in question 19.

## Q20-21: Disease Relapse or Progression

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### Question 20: Was a disease relapse or progression detected since the date of last report?

Disease relapse or progression can be documented by a variety of methods including molecular, flow cytometry, cytogenetic/fluorescent in situ hybridization (FISH), hematological/radiographic or clinical. Answer “yes” if disease relapse or progression were documented by anyone of the methods and continue with question 21.

If a disease relapse or progression was not documented, answer “no” and continue to question 22.

### Question 21: Date documented:

Report the date (YYYY-MM-DD) of the relapse or progression detected since the date of the last report.

# Q22-26: New Malignancy, Lymphoproliferative or Myeloproliferative Disease/Disorder

- ! Report new malignancies that are different than the disease / disorder for which cellular therapy was performed. Do not include relapse, progression or transformation of the same disease subtype.

## \* Questions 22-26 New Malignancy

For scenarios where both HCT and CT forms will be submitted at the same time, there are duplicate questions across the F2100 and F4000. To reduce the reporting burden, duplicated questions on the Cell Therapy forms are disabled. This includes new malignancy reported on F4100.

**Question 22: Did a new malignancy, myelodysplastic, myeloproliferative, or lymphoproliferative disease / disorder occur that is different from the disease / disorder for which the cellular therapy was performed? (include clonal cytogenetic abnormalities, and post-transplant lymphoproliferative disorders):**

Indicate whether a new or second primary malignancy, including lymphoproliferative disorder, or myeloproliferative disorder, has developed. Do not report recurrence, progression, or transformation of the recipient's primary disease (disease for which the cellular therapy was performed) or relapse of a prior malignancy.

New malignancies, lymphoproliferative disorders, and myeloproliferative disorders include but are not limited to:

- Skin cancers (basal, squamous, melanoma)
- New leukemia
- New myelodysplasia
- Solid tumors
- PTLD (post-transplant lymphoproliferative disorder) report as lymphoma or lymphoproliferative disease

The following should **not** be reported as new malignancy:

- Recurrence of primary disease (report as relapse or disease progression)

- Relapse of malignancy from recipient's pre-cellular therapy medical history
- Breast cancer found in other (i.e., opposite) breast (report as relapse)
- Post-cellular therapy cytogenetic abnormalities associated with the pre-cellular therapy diagnosis (report as relapse)

### **Questions 23-26 Reporting more than one new malignancy**

FormsNet3<sup>SM</sup> application: Complete questions 23-26 for each new malignancy diagnosed since the date of last report. by adding an additional instance in the FormsNet application.  
Paper form submission: Copy and complete questions 23-26 to report each new malignancy diagnosed since the date of last report.  
The submission of a pathology report or other supportive documentation for each reported new malignancy is strongly recommended.

#### **Question 23 & 24: Specify the new malignancy:**

Select from the list the new malignancy diagnosed since the date of the last report. If “other new malignancy” is selected, specify in question 24. Continue with question 25.

#### **Question 25: Date of diagnosis:**

Report the date (YYYY-MM-DD) of diagnosis of the new malignancy reported in question 23 or 24.

#### **Question 26: Was the new malignancy donor / cell product derived?**

Answer “yes” if testing on the new malignancy sample determined it was derived from the donor or cell product. Answer “no” if testing on the new malignancy sample determined it was not derived from the donor or cell product.

If testing was not performed to determine if the new malignancy was not of donor or cell product origin, answer “not done”.

## Q27-42: Persistence of Cells

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

### **Question 27: Were tests performed to detect persistence of the cellular product since the date of last report?**

Methods such as PCR assays, flow cytometry (immunophenotyping) or chimerism studies can be used to detect persistence of the cellular product in the recipient.

If tests were performed to detect persistence of the cellular product since the date of the last report, select “yes” and continue with question 28.

If tests were not performed to detect persistence of the cellular product since the date of the last report, select “no” and continue with question 43.

### **Question 28: Was persistence evaluated by molecular assay (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.

Indicate whether molecular assay testing was performed within the reporting period. If “yes”, continue with question 29. If “no”, continue with question 33.

### **Question 29: Date Sample collected:**

Report the date (YYYY-MM-DD) the sample was collected for molecular assay. If multiple studies were performed in the reporting period, report the most recent testing that documents persistence of cells by molecular assay. If all the molecular assays are negative for persistence of cells, then report the most recent test performed in the reporting period.

**Question 30 & 31: Specify the cell source:**

Select bone marrow, peripheral blood, tumor, or other source as the cell source of the sample collected for evaluation by molecular assay. If other, specify in question 31.

**Question 32: Were the infused cells detected?**

Select “yes” if the infused cells were detected by molecular assay.

Select “no” if the infused cells were not detected by molecular assay.

**Question 33: Was persistence evaluated by flow cytometry testing (immunophenotyping)?**

Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tumor (tissue) preparations for multiple unique cell characteristics.

Indicate whether flow cytometry testing was performed within the reporting period. If “yes”, continue with question 34. If “no”, continue with question 38.

**Question 34: Date sample collected:**

Report the date (YYYY-MM-DD) the sample was collected for flow cytometry testing (immunophenotyping). If multiple studies were performed in the reporting period, report the most recent testing that documents persistence of cells by flow cytometry. If all the flow cytometry tests are negative for persistence of cells, then report the most recent test performed in the reporting period.

**Question 35 & 36: Specify the cell source:**

Select bone marrow, peripheral blood, tumor, or other source as the cell source of the sample collected for evaluation by flow cytometry. If other, specify in question 36.

**Question 37: Were the infused cells detected?**

Select “yes” if the infused cells were detected by flow cytometry testing (immunophenotyping).

Select “no” if the infused cells were not detected by flow cytometry testing (immunophenotyping).

**Question 38: Was persistence evaluated by chimerism studies?**

Different types of blood cells and a variety of laboratory tests can be used to determine if a chimera (presence of both the cellular product and host derived cells) exists.

Indicate whether chimerism studies were performed within the reporting period. If “yes”, continue with question 39. If “no”, continue with question 43.

**Question 39: Date sample collected:**

Report the date (YYYY-MM-DD) the sample was collected for chimerism studies. If multiple studies were performed in the reporting period, report the most recent testing that documents persistence of cells by chimerism studies. If all the chimerism studies are negative for persistence of cells, then report the most recent test performed in the reporting period.

**Question 40 & 41: Specify the cell source:**

Select bone marrow, peripheral blood, tumor, or other source as the cell source of the sample collected for evaluation by chimerism studies. If other, specify in question 41.

**Question 42: Were the infused cells detected?**

Select “yes” if the infused cells were detected by chimerism studies.

Select “no” if the infused cells were not detected by chimerism studies.



# Q43-113: Cytokine Release Syndrome

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## Question 43: Did the recipient develop Cytokine Release Syndrome (CRS) since the date of last report?

Cytokine Release Syndrome (CRS) is defined by development of a constellation of signs and symptoms that are seen after the infusion of monoclonal antibodies or cellular therapy products. It results from the sometimes rapid release of several inflammatory cytokines as a consequence of immune response triggered by a drug (i.e. monoclonal antibody) or cellular product. This rapid cytokine release into the circulation results in fever, nausea, chills, hypotension, tachycardia, asthenia, headache, rash, sore throat, respiratory failure and death. This section attempts to collect different clinical and laboratory information to understand the severity of this event.

If the recipient developed CRS since the date of last report, select “yes” and continue with question 44. If the recipient did not develop CRS, continue with question 115.

## Question 44: Date of diagnosis:

Report the date when the first symptom of CRS was documented by a physician or other health care provider in the progress note or chart.

## Question 45-91: Specify if the recipient has developed any of the following since the date of last report:

Specify if the recipient developed any of the following symptoms and report the date of diagnosis (YYYY-MM-DD) of each symptom.

Most of the symptoms below can be unspecific and should be marked only if there is a clinical suspicion that the sign or symptom was associated with the administration of the cellular product.

### **Fevers (>100.4 F or > 38 C)**

**Rigors:** A sudden feeling of cold with shivering accompanied by a rise in temperature, often with sweating, especially at the onset or height of a fever.

**Malaise/Fatigue:** Malaise is a general feeling of discomfort, illness, or uneasiness whose exact cause is difficult to identify. Fatigue is extreme tiredness, typically resulting from mental or physical exertion or illness.

**Anorexia:** A lack or loss of appetite for food.

**Myalgias/artralgias:** Myalgia is pain in a muscle or group of muscles and artralgia is pain in a joint.

**Nausea/vomiting:** Nausea is a feeling of sickness with an inclination to vomit. Vomiting is the expelling of undigested food or other content through the mouth.

**Other constitutional symptom:** Includes weight loss, hyperhidrosis, chronic pain, etc.

**Hypoxia requiring minimal supplemental oxygen (FiO<sub>2</sub><40%):** A lower than normal concentration of oxygen in arterial blood requiring supplemental oxygen of <40% FiO<sub>2</sub>.

**Hypoxia requiring more than minimal supplemental oxygen (FiO<sub>2</sub>>40%):** A lower than normal concentration of oxygen in arterial blood requiring supplemental oxygen of >40% FiO<sub>2</sub>.

**Hypotension requiring therapy:** Abnormally low blood pressure requiring treatment with volume resuscitation or vasopressors such as norepinephrine or dopamine.

**Grade 4 organ toxicity:** Liver, lungs, heart, kidneys, gastrointestinal, musculoskeletal, neurologic, or other organ.


### Question 92: Was therapy given? (for CRS)

Indicate “yes” if the recipient received therapy for CRS and continue with question 93.

Indicate “no” if no therapy was given for CRS and continue with.

### Question 93-97: Specify therapy given for CRS:

Indicate “yes” or “no” for each drug listed. If “other therapy” was given, specify in question 97.

 Specify the maximum lab results since the date of last report

### Question 98-100: Interleukin-6

Interleukin-6 is a pro-inflammatory cytokine derived from macrophages and endothelial cells that increases synthesis and secretion of immunoglobulins by B lymphocytes.

Indicate if the lab value is “known” or “unknown” in question 98. If known, report the value in question 99 and the date (YYYY-MM-DD) the sample was collected in question 100.

### Question 101-103: Interferon gamma IFN- $\gamma$ :

Interferon gamma is a pro-inflammatory cytokine produced by macrophages and T-cells that is involved in the regulation of the immune system and activation of phagocytes.

Indicate if the lab value is “known” or “unknown” in question 101. If known, report the value in question 102 and the date (YYYY-MM-DD) the sample was collected in question 103.

**Question 104-106: Soluble interleukin-2 receptor  $\alpha$  (sIL2RA or soluble CD25):**

Interleukin-2 receptor alpha or CD25 can shed from the surface of cells during inflammatory conditions. This test detects soluble or circulating sIL2RA.

Indicate if the lab value is “known” or unknown” in question 104. If known, report the value in question 105 and the date (YYYY-MM-DD) the sample was collected in question 106.

**Question 107-109: Total serum ferritin**

Ferritin is an acute phase reactant and is often found in high concentration in highly inflammatory conditions.

Indicate if the lab value is “known” or unknown” in question 107. If known, report the value in question 108 and the date (YYYY-MM-DD) the sample was collected in question 109.

**Question 110-112: C-reactive protein**

C-reactive protein (CRP) is a protein produced by the liver and found in the blood. C-RP levels increase with tissue injury or trauma, infection or inflammation. CRP is also highly associated with IL-6 levels.

Indicate if the lab value is “known” or unknown” in question 110. If known, report the value in question 111 and the date (YYYY-MM-DD) the sample was collected in question 112.

**Question 113 & 114: Did cytokine release syndrome resolve?**

If the cytokine release syndrome resolved, select “yes” and report the date (YYYY-MM-DD) in question 114.

# Q115-126: Neurotoxicity

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## Question 115: Did neurotoxicity occur since the date of last report?

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

Indicate “yes” if neurotoxicity occurred and continue with question 116. Indicate “no” if neurotoxicity did not occur or “unknown” if unsure whether neurotoxicity occurred and continue with question 127.

## Question 116: Date of diagnosis:

Report the date when the first symptom of neurotoxicity was documented by a physician or other health care provider in the progress note or chart.

## Question 117-124: Specify symptoms of neurotoxicity:

Indicate “yes” or “no” for each symptom of neurotoxicity.

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

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

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

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

**Hemiparesis:** Paralysis of one side of the body.

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

## Question 125 & 126: Did neurotoxicity resolve?

If the cellular therapy associated neurotoxicity resolved, select “yes” and report the date (YYYY-MM-DD) in question 126. Resolution means complete normalization of neurologic function. It is possible that patients might remain with residual neurologic dysfunction which would not qualify as complete resolution of this complication.

## Q127-130: Functional Status

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**!** This section focuses on fertility. This is an important section due to the possibility of some genetic modified cells persisting and possibly circulating to the fetus.

### **Question 127: Was the recipient pregnant at any time in this reporting period? (Female only)**

Indicate “yes” if the female recipient was pregnant at any time during the reporting period and continue with question 129. Indicate “no” if the female recipient was not pregnant at any time during the reporting period.

### **Question 128: Was the recipient’s female partner pregnant at any time in this reporting period? (Male only)**

Indicate “yes” if the male recipient’s partner was pregnant at any time during the reporting period. Indicate “no” if the male recipient’s partner was not pregnant at any time during the reporting period.

### **Question 129: Was the recipient or recipient’s partner still pregnant at the date of last contact?**

Indicate “yes” if the female recipient or recipient’s female partner were still pregnant at the date of last contact. Indicate “no” if the female recipient or recipient’s female partner was not pregnant at the date of last contact and continue with question 130.

### **Question 130: Specify the outcome of pregnancy:**

Indicate if the pregnancy ended in a “live birth”, “intrauterine fetal death”, “spontaneous abortion”, “elected abortion” or if the outcome is “unknown”.