

4100: Cellular Therapy Essential Data Follow-Up

This form must be completed for all recipients of cellular therapy (non-HCT), including post-HCT “DCI/DLI” infusions. For recipients of hematopoietic cellular transplants, complete the appropriate HCT follow up form.

The Post-Cellular Therapy Essential Data (Post-CTED) follow up form 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 toxicities (e.g. cytokine release syndrome, neurotoxicity) and fertility information.

The Post-CTED form must be completed at the following time points: 100 days, six months, and annually post-cellular therapy. The follow up reporting schedule is determined by the product, being genetically modified or not. The structure of the Post-CTED is such that each form should fit on a timeline with distinct start and stop dates that do not overlap any other forms, except in the case where an HCT is also received.

In scenarios where both HCT and cellular therapy forms are being completed, completion of this form should be based on the time period after cellular therapy infusion date (i.e. 100 days after the cellular therapy infusion date).

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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
1/ 23/ 18	4100: Cellular Therapy Essential Data Follow- Up	Add	Added HCT and CT note box above question 44.
11/ 15/ 17	4100: Cellular Therapy Essential Data Follow- Up	Modify	Replaced description of grade 4 organ toxicity provided in the instructions for Questions 82-138. Grade 4 organ toxicity: <i>As defined by the CTCAE criteria , grade 4 toxicity represents life-threatening consequences and urgent intervention is indicated Liver, lungs, heart, kidneys, gastrointestinal, musculoskeletal, neurologic, or other organ. Based on the CTC criteria</i>
7/ 25/ 17	4100: Cellular Therapy Essential Data Follow- Up	Modify	Version 2 of the 4100: Cell Therapy Essential Data Follow-Up section of the Forms Instructions Manual released. Version 2 corresponds to revision 2 of the Form 4100.

Q1-6: Survival

* Survival status

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 Cellular 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 FormsNet3SM

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 & Subsequent Infusion

The date of contact reported depends on the regulatory requirements of the product and whether follow up is required.

Example 3. *The recipient receives a subsequent HCT or cellular therapy.*

The recipient had a cellular therapy on 1/1/14 and was seen regularly through the first 100 days. During the 6 month reporting period, the recipient goes on to receive an HCT or subsequent cellular therapy.

What to report

Regulatory requirements specify 15 years of follow up data be collected on genetically modified cellular therapy products: The date of contact reported should be appropriate to the time frame of the form being completed (e.g. 6 months)

Cellular therapy products where regulatory requirements do not specify follow up reporting: The date of contact reported will be the date prior to the start of the preparative regimen for the subsequent infusion (in cases where no prep is given, it is the day prior to the infusion).

Date of Contact & Death

In the case of recipient death, 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 4. *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 5. *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)

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 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. If the cause of death is reported as "other infection", "other pulmonary syndrome", "multiple organ failure", "other organ failure", "other hemorrhage", "other vascular" or "other cause", specify the other cause in question 4.

Form 2900 Recipient Death form is not required for cellular therapy recipients.

Question 5-6: Contributing cause of death: (check all that apply)

Report any additional causes of death, select all causes that are applicable. All contributing causes of death are important for analysis of cellular therapy outcomes. If the contributing cause of death is reported as "other infection", "other pulmonary syndrome", "multiple organ failure", "other organ failure", "other hemorrhage", "other vascular" or "other cause", specify the other cause in question 6.

Q7-11: Subsequent Cellular Infusions

* Subsequent Cellular Infusions

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

Question 7: Has the recipient started a new course of cellular therapy (unplanned) since the date of the last report?

If the recipient started a new course of cellular therapy (unplanned) that is different than the course reported on the form 4000, answer “yes” and continue with question 8.

In cases where the course of cellular therapy is being given post-HCT and HCT follow up forms are also being completed, and where the cellular therapy course overlaps two HCT reporting periods, the new course only needs to be reported once on the HCT follow up forms.

Example- the new course of cellular therapy consisted of multiple infusions that happened at the end of the 6 month reporting period into the beginning of the 1 year HCT reporting period. The new course of cellular therapy should be reported only on the 6 month form.

If the recipient has not received a new course of cellular therapy (unplanned) since the date of last report continue with question 10.

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

If additional infusions were given for the same indication per protocol, do not report those here. Please update question 30 on form 4000 with the correct number of infusions given per protocol. Each infusion requires a separate form 4006.

If the reason for the new course of cellular therapy was failure to respond or in response to disease assessment, or for a new indication, report the event date in question 9.

Question 9: Date of cellular therapy:

Report the date (YYYY-MM-DD) of the new course of cellular therapy (unplanned). If the new course of cellular therapy includes multiple infusions, the date of the first infusion should be reported here. This will require completion of a new form 4000.



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 a subsequent HCT reported on F4100.

Question 10 & 11: 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 (YYYY-MM-DD) the date of HCT in question 11 and also complete CIBMTR HCT form 2400.

If the recipient did not receive an HCT, continue with question 12.

Q12-14: Best Response to Cellular Therapy

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

Question 12: 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 and disorders.

For malignant diseases, appropriate responses would be:

- complete response
- partial response
- no response
- disease progression
- unknown

For non-malignant disorders, appropriate responses would be:

- normalization of organ function
- partial normalization of organ function
- no response
- worsening of organ function
- unknown

If the indication is infection, the appropriate responses would be:

- complete response
- partial response
- no response
- unknown

Table 1. Examples of Best Response to Cellular Therapy

Indication	Partial Response	Complete Response
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Promote stem cell engraftment	-Neutrophil engraftment without platelet engraftment -Platelet engraftment without neutrophil engraftment	Engraftment occurs
Suboptimal donor chimerism (post-HCT)	Increase in chimerism but not 100% donor	100% donor chimerism
Immune Reconstitution (post-HCT)	N/A	CD3 >200/mm ³
GVHD prophylaxis (with HCT)	N/A	N/A
GVHD treatment (post-HCT)	-Improvement but not resolution of symptoms -Remains on immune suppression	-Resolution of symptoms -Able to wean immune suppression
Prevent disease relapse	N/A	N/A
Relapsed, persistent or progressive disease (post-HCT)	Improvement in disease burden, but with persistent disease	No evidence of disease
Infection treatment	Decrease in infectious load without resolution	Undetectable infection
Infection prophylaxis	N/A	N/A
B-cell lymphoproliferative disorder (PTLD, EBV lymphoma)	Improvement in disease burden, but with persistent disease	No evidence of disease
Autoimmune Disease	Improvement in organ function but with residual organ dysfunction	Normalization of organ function
Cardiovascular Disease Musculoskeletal Disorder Neurologic Disease Ocular Disease Pulmonary Disease	Improvement in organ function but with residual organ dysfunction	Normalization of organ function
Solid Tumor	Improvement in disease burden, but with persistent disease	No evidence of disease
Malignant Hematologic Disorder	Improvement in disease burden, but with persistent disease	Hematologic Remission or MRD negative
Non-Malignant Disorder	Persistent Disease	Resolution of Disease Process

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 13-14: Was the date of best response previously reported?

If the date of best response was previously reported, select “yes” and continue with question 14. **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 (YYYY-MM-DD) in question 14.

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

Q15-16: Disease Relapse or Progression



Questions 15-16

This section is applicable to malignant disease only.

Question 15-16: 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), radiographic or hematological/clinical. Answer “yes” if disease relapse or progression were documented by any one of the methods and report the date (YYYY-MM-DD) of the relapse or progression detected since the date of the last report in question 16.

If a disease relapse or progression was not documented, answer “no” and continue to question 17.

Q17-21: New Malignancy, Lymphoproliferative or Myeloproliferative Disease / Disorder



New Malignancies

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.



HCT and Cellular Therapy

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, duplicate questions on the Cell Therapy forms are disabled. This includes a new malignancy reported on F4100.

Question 17: 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 18-21 Reporting more than one new malignancy

FormsNet3SM application: Complete questions 18-21 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 18-21 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 18-19: 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 19. Continue with question 20.

Question 20: Date of diagnosis:

Report the date (YYYY-MM-DD) of diagnosis of the new malignancy reported in question 18 or 19.

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 21: 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”.

Q22-43: Persistence of Cells

Questions 22-43

This section pertains to the evaluation of persistence of a cellular product in the recipient. It only applies to genetically modified cellular products.

Question 22: 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 immunohistochemistry 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 23.

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 44.

Question 23: 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 24. If “no”, continue with question 28.

Question 24: Date Sample collected:

Report the date (YYYY-MM-DD) the sample was collected for molecular assay. If multiple tests were performed in the reporting period and

- all tests were negative: report the first negative test result
- there were positive and negative results: report the date of the last positive test.

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 25-26: 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 the source is “other”, specify in question 26.

Question 27: 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 28: Was persistence evaluated by flow cytometry testing (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.

Indicate whether flow cytometry 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 flow cytometry testing (immunophenotyping). If multiple tests were performed in the reporting period and

- all tests were negative: report the first negative test result
- there were positive and negative results: report the date of the last positive test

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 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 flow cytometry. If other, specify in question 31.

Question 32: 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 33: Was persistence evaluated by immunohistochemistry?

Immunohistochemistry is a process that uses antibodies to test for certain antigens (markers) in a sample. When the antibodies bind to the antigen in the tissue sample, the enzyme or dye is activated, and the antigen can then be seen under a microscope.

Indicate whether immunohistochemistry 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 immunohistochemistry studies. If multiple tests were performed in the reporting period and

- all tests were negative: report the first negative test result
- there were positive and negative results: report the date of the last positive test

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 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 immunohistochemistry testing. If other, specify in question 36.

Question 37: Were the infused cells detected?

Select “yes” if the infused cells were detected by immunohistochemistry testing. Select “no” if the infused cells were not detected by immunohistochemistry testing.

Question 38: Was persistence evaluated by other method?

If persistence of cells was tested by a method not listed above, select “yes” and continue with question 39. If “no”, continue with question 44.

Question 39: Specify other method:

Specify the other method used to evaluate persistence of cells.

Question 40: Date sample collected:

Report the date (YYYY-MM-DD) the sample was collected for the other method. If multiple tests were performed in the reporting period and

- all tests were negative: report the first negative test result
- there were positive and negative results: report the date of the last positive test

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 41-42: Specify the cell source:

Select bone marrow, peripheral blood, tumor, or other source as the cell source of the sample collected for evaluation by other method. If other, specify in question 42.

Question 43: Were the infused cells detected?

Select “yes” if the infused cells were detected by other method. Select “no” if the infused cells were not detected by other method.

Q44-63: Graft vs. Host Disease

Autologous Infusions

Questions 44-63 should be completed for allogeneic infusions only. If this was an autologous infusion, continue to question 64.

HCT and CT

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 Cellular Therapy forms are disabled. This includes GVHD reported on F4100 .

Graft versus Host Disease (GVHD) is an immunological phenomenon resulting from the reaction of donor immune cells against major or minor histocompatibility antigens of the recipient. GVHD is primarily caused by donor-derived T-cells. Very rarely, GVHD may occur due to autologous reactivity (autologous GVHD), third party transfusions, or with identical twin transplantation.

Factors influencing the severity of GVHD are related to three main categories: 1) donor or graft, 2) recipient, and 3) treatment. The most influential donor/graft factor is the degree of genetic disparity between the donor and the recipient (HLA match), but other risk factors include female donor to male recipient, donor parity, older donors, and T-cell dose. The occurrence of acute GVHD becomes a risk factor for the development of chronic GVHD. Recipient age and prior infections are also factors.

In the past, GVHD was classified as acute or chronic based on its time to diagnosis following transplant, and other clinical and histological (biopsy or post-mortem) features. Today, there has been increased recognition that acute and chronic GVHD are not dependent upon time since HCT, so determination of acute or chronic should rest on clinical and histologic features. However, organ staging and overall grade should only be calculated from the clinical picture, not histology. Acute GVHD usually begins between 10 and 40 days after HCT but can appear earlier or later. The organs most commonly affected by acute GVHD are the skin, gut, or liver. Other sites, such as the lung, may be involved.

Acute / Chronic GVHD

If acute GVHD is diagnosed prior to chronic GVHD, report the diagnosis information, maximum severity of any symptoms, and treatment administered up to the date of diagnosis of chronic GVHD in the acute GVHD section of the form (questions 44-55). Do not include

any signs, symptoms, or treatment occurring on or after the onset of chronic GVHD when completing the acute GVHD section.

Report any new or persistent acute GVHD symptoms occurring on or after the onset of chronic GVHD only in the chronic GVHD section. If chronic GVHD was diagnosed in a prior reporting period, report “no” for questions 44 and 46 in each subsequent reporting period. See reporting scenarios included in question 44.

Question 44: Did acute GVHD develop since the date of last report?

Questions 44 and 46 on the Cellular Therapy Essential Data Follow-Up Form are meant to capture whether the recipient had active symptoms of acute GVHD during the reporting period. If the recipient had active acute GVHD during the reporting period, either question 44 or question 46 must be answered “yes” unless there has been a prior / concurrent diagnosis of chronic GVHD (see note above question 44). There will not be a situation where “yes” is reported for both question 44 and question 46. If question 44 is answered yes and a diagnosis date has been reported in question 45, question 46 will be disabled in FormsNet3SM. Centers should report “yes” for question 44 to indicate the recipient developed acute GVHD in the following scenarios:

- Acute GVHD is diagnosed for the first time during the reporting period.
- An acute GVHD flare is diagnosed during the current reporting period and all of the following conditions are met:
 - The recipient’s prior acute GVHD symptoms did **not** persist from the prior reporting period into the beginning of the current reporting period.
 - The flare is diagnosed **after at least 30 days** without any active acute GVHD symptoms.
 - The recipient was not diagnosed with chronic GVHD on or before the date of the flare (see note above question 44).

If the recipient does have active acute GVHD during the reporting period, but does not match either of the scenarios above, the center will likely need to report “no” for question 44 and “yes” for question 46. Question 46 is intended to capture acute GVHD which has continued from a prior reporting period. This includes any flares which do not meet the above conditions. The intent of classifying GVHD episodes as newly developed or persistent is to avoid having centers re-report diagnosis information which has been captured on a prior form. Refer to the Acute GVHD Diagnosis Scenarios below to see examples of how to answer questions 44 and 46.

Report “no” for questions 44 and 46 if the recipient had no active acute GVHD symptoms during the reporting period **OR** all acute GVHD signs / symptoms during the reporting period occurred after a diagnosis of chronic GVHD (see note above question 44).

Indicate “unknown” if there is no information about the recipient’s GVHD status for the reporting period. This option should be used sparingly and only when no judgment can be made about the presence or absence of GVHD in the reporting period.

Acute GVHD Diagnosis Scenarios:

A. A recipient receives a cellular therapy infusion of an allogeneic product on 1/1/2015 and develops acute GVHD which is clinically diagnosed on 2/1/2015. At least one of their symptoms, attributed to acute GVHD, persists beyond the 100 day date of contact which is 4/5/2015. Treatment continues and symptoms completely resolve on 5/1/2015. Immunosuppression is tapered until a flare of acute GVHD is diagnosed on 5/25/2015. Immunosuppression is given and symptoms quickly resolve with no active acute GVHD beginning 6/10/2015. The six month date of contact is 6/20/2015. Another flare of acute GVHD is clinically diagnosed on 8/15/2015.

100 Day Post-TED Form:

Question 44: Report “yes” to indicate a new clinical diagnosis of acute GVHD.

Question 45: Report the initial date of diagnosis (2/1/2015).

Question 46: Leave blank. This question will be skipped whenever a diagnosis date has been entered in question 45.

Questions 47-53: Answer these questions based on the assessments performed at the time of diagnosis (2/1/2015).

Six Month Post-TED Form:

Question 44: Report “no” to indicate acute GVHD persists from a previous report. Note, the flare of acute GVHD was < 30 days from symptoms resolution so it doesn’t count as a new reportable episode.

Question 45: Leave blank. This question will be skipped whenever question 44 is answered “no.”

Question 46: Report “yes” to indicate GVHD persists from a previous report.

Questions 47-53: Leave blank. Answering “yes” for question 46 prevents the center from re-reporting diagnosis information already captured on the 100 day form.

One Year Post-Infusion Data Form:

Question 44: Report “yes” to indicate a flare of acute GVHD occurred at least 30 days after resolving during a prior reporting period.

Question 45: Report the diagnosis date of the flare occurring during the reporting period (8/15/2015).

Question 46: Leave blank. This question will be skipped whenever a diagnosis date has been entered in question 45.

Questions 47-53: Answer these questions based on the assessments performed at the time of diagnosis of the flare of acute GVHD (8/15/2015).

B. A recipient receives a cellular therapy infusion of an allogeneic on 1/1/2015 and develops acute skin GVHD on 2/1/2015 and then chronic eye GVHD on 3/1/2015. Both acute and chronic symptoms resolve by the 100 day date of contact (4/5/2015). While tapering their immunosuppression, the recipient has a flare of their acute skin GVHD on 5/30/2015. Treatment continues and symptoms completely resolve by the six month date of contact (6/20/2015).

100 Day Post-Infusion Data Form:

Question 44: Report “yes” to indicate a new clinical diagnosis of acute GVHD.

Question 45: Report the initial date of diagnosis (2/1/2015).

Question 46: Leave blank. This question will be skipped whenever a diagnosis date has been entered in question 45.

Questions 47-53: Answer these questions based on the assessments performed at the time of diagnosis (2/1/2015).

Six Month Post-Infusion Data Form:

Question 44: Report “no” to indicate acute GVHD did not develop during the reporting period.

Question 45: Leave blank. This question will be skipped whenever question 44 is answered “no.”

Question 46: Report “no” to indicate acute GVHD did not persist from a previous report.

If chronic GVHD has been diagnosed in a prior reporting period, report “no” for questions 44 and 46.

Any new or persistent acute GVHD symptoms occurring after the onset of chronic GVHD must be reported in the chronic GVHD section of the form. Do not include any signs, symptoms, or treatment occurring on or after the onset of chronic GVHD when completing the acute GVHD section. This instruction has been provided in the note above question 44.

Question 45: Date of acute GVHD diagnosis:

Report the date of clinical diagnosis of acute GVHD. The clinical diagnosis date may not necessarily be the date the symptoms began (example: the recipient developed a rash one week prior to the physician clinically diagnosing acute skin GVHD). If the clinical diagnosis is documented, but the diagnosis date is unclear, obtain documentation from the primary physician confirming the clinical diagnosis date.

If the recipient developed more than one episode of acute GVHD in the same reporting period, report the date of onset of the first episode of acute GVHD.

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 46: Did acute GVHD persist since the date of last report?

Question 46 will only be enabled in FormsNet3SM if the center has reported “no” for question 44 and, therefore, has not reported a date of diagnosis in question 45. If prompted to answer question 46, report “yes” if acute GVHD was diagnosed in a prior reporting period and any of the following conditions are met:

- The recipient’s acute GVHD symptoms have been active since diagnosis and continue to be active during the current reporting period (i.e., no period of resolution or quiescence since diagnosis).
- The recipient’s acute GVHD symptoms had resolved before the first day of the current reporting period, but a flare occurred within 30 days of symptom resolution / quiescence.
- The recipient was not diagnosed with chronic GVHD on or before the date of the flare (see note above question 44).

Report “no” for questions 44 and 46 if the recipient had no active acute GVHD symptoms during the reporting period and all acute GVHD signs / symptoms during the reporting period occurred after a diagnosis of chronic GVHD (see note above question 44).

Indicate “unknown” if there is no information about the recipient’s GVHD status for the reporting period. This option should be used sparingly and only when no judgment can be made about the presence or absence of GVHD in the reporting period.

Question 47: Overall grade of acute GVHD at diagnosis:

Indicate the overall grade of acute GVHD at the time of diagnosis. The acute GVHD grading scale is based on clinical evidence (physician observation), not histology. Pathology reports sometimes list a histologic grade of GVHD. Do not report the histologic grade. GVHD scoring and grading is based on clinical severity, not histologic severity. Biopsy of affected organs allows for more precise diagnosis as to the presence or absence of GVHD. However, overall grading remains clinical and is based on the criteria published by Przepiorka et al., *Bone Marrow Transplant* 1995; 15(6):825-8, see the GVHD Grading and Staging table below.

If acute GVHD was present, but the grade at diagnosis was not documented and it cannot be determined from the grading and staging table, report “not applicable.”

Examples may include:

- Only elevated liver function tests without increased bilirubin
- Any other organ involvement without skin, liver, or gut symptoms attributable to GVHD
- Lower intestinal tract involvement where the stage cannot be determined in select scenarios (see lower intestinal tract involvement description below)

Upper GI GVHD

If the recipient only has upper GI GVHD during the reporting period, report this as overall grade II. This may differ from prior instructions regarding how to report upper GI GVHD.

GVHD Grading and Staging

Stage	Skin	Liver	Gut
1	Rash on <25% of skin ¹	Bilirubin 2-3 mg/dl ²	Diarrhea > 500 ml/day ³ or persistent nausea ⁴ <i>Pediatric</i> : 280-555 ml/m ² /day or 10-19.9 mL/kg/day
2	Rash on 25-50% of skin	Bilirubin 3-6 mg/dl	Diarrhea >1000 ml/day <i>Pediatric</i> : 556-833 ml/m ² /day or 20-30 mL/kg/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dl	Diarrhea >1500 ml/day <i>Pediatric</i> : >833 ml/m ² /day or > 30 mL/kg/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus
Grade ⁵			
I	Stage 1-2	None	None
II	Stage 3	Stage 1	Stage 1
III	—	Stage 2-3	Stages 2-4
IV ⁶	Stage 4	Stage 4	—

¹ Use “Rule of Nines” ([Percent Body Surfaces table](#)) or burn chart to determine extent of rash.

² Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

³ Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

⁴ Persistent nausea with or without histologic evidence of GVHD in the stomach or duodenum.

⁵ Criteria for grading given as minimum degree of organ involvement required to confer that grade.

⁶ Grade IV may also include lesser organ involvement with an extreme decrease in performance status

Question 48-53: List the stage for each organ at diagnosis of acute GVHD:

Skin: Select the stage that reflects the body surface area involved with a maculopapular rash attributed to acute GVHD at the time of acute GVHD diagnosis or flare in the reporting period. See the Percent Body Surfaces table below to determine the percent of body surface area involved with a rash. Do not report ongoing rash not attributed to acute GVHD at the time of acute GVHD diagnosis or flare.

Percent Body Surfaces

p(#Body). **Percent Body Surfaces**

Body Area	Percent	Total Percentage
Each Arm	9%	18%
Each Leg	18%	36%
Chest & Abdomen	18%	18%
Back	18%	18%
Head	9%	9%
Pubis	1%	1%

Lower intestinal tract (use mL/day for adult recipients and mL/m2/day for pediatric recipients): Select the stage that reflects the volume of diarrhea attributed to acute GVHD at the time of acute GVHD diagnosis or flare in the reporting period. Use mL/day for adult recipients and mL/m2/day for pediatric recipients. Input and output records may be useful in determining the volume of diarrhea. Do not report ongoing diarrhea not attributed to acute GVHD at the time of acute GVHD diagnosis or flare.

If diarrhea is attributed to acute GVHD during the reporting period, but the volume of stool output is not documented, report “stage 0” for lower intestinal tract involvement. In this case, report “not Applicable” for the overall grade unless stage 4 acute skin GVHD, stage 4 acute liver GVHD, or an extreme decrease in performance status was also documented at the time point being reported (at diagnosis or maximum grade during the reporting period). Report an overall grade of IV if stage 4 acute skin GVHD, stage 4 acute liver GVHD, or an extreme decrease in performance status is documented at the time point being reported (see GVHD Staging and Grading Table). Report overall grade III if stage 2-3 liver involvement is documented at the time point being reported and there is no evidence of grade IV GVHD.

Upper intestinal tract: Select the stage that reflects the presence of persistent nausea or vomiting attributed to acute GVHD at the time of acute GVHD diagnosis or flare in the reporting period. Do not report ongoing nausea or vomiting not attributed to acute GVHD at the time of acute GVHD diagnosis or flare.

Liver: Select the stage that reflects the bilirubin level attributed to acute GVHD at the time of acute GVHD diagnosis or flare in the reporting period. Do not report ongoing hyperbilirubinemia not attributed to acute GVHD at the time of acute GVHD diagnosis or flare.

For recipients who have a normal bilirubin level with elevated transaminase levels attributed to acute GVHD, report this in “Other clinical organ involvement.”

Other site(s) involved with acute GVHD: Indicate whether acute GVHD affected an organ other than skin, upper GI, lower GI, or liver manifesting with hyperbilirubinemia. This includes transaminitis attributed to acute GVHD. Report only other organ involvement at the time of acute GVHD diagnosis or flare in the reporting period. Do not report symptoms ongoing but not attributed to acute GVHD at the time of acute GVHD diagnosis or flare. Specify the other organ system involvement in question 53. If reporting transaminitis under “other site,” write in “transaminitis” rather than “liver” when specifying the site. This will prevent queries regarding incorrectly reporting liver GVHD (with bilirubin elevation) under “other site.”

Question 54: Maximum Overall Grade of Acute GVHD:

Indicate the overall maximum grade of acute GVHD since the date of the last report. Grading is based on clinical evidence (physician observation), not histology. Pathology reports sometimes list a histologic grade of GVHD. Do not report the histologic grade. GVHD scoring and grading is based on clinical severity, not histologic severity. Biopsy of affected organs allows for more precise diagnosis as to the presence or absence of GVHD. However, overall grading remains clinical and is based on the criteria published by Przepiorka et al., *Bone Marrow Transplant* 1995; 15(6):825-8; see the GVHD Grading and Staging table above.

If chronic GVHD was diagnosed during the reporting period, report the maximum severity of acute GVHD prior to the onset of chronic GVHD. See question 44 for further instructions. Acute GVHD grading scenario D below has been provided for further clarification.

Report the recipient’s maximum acute GVHD grade in the reporting period; this may differ from the grade at diagnosis or may be the same. If acute GVHD was present, but the maximum grade was not documented and it cannot be determined from the grading and staging table, report “not applicable.”

Examples may include:

- Only elevated liver function tests without increased bilirubin

- Any other organ involvement without skin, liver, or gut symptoms attributable to GVHD
- Lower intestinal tract involvement where the stage cannot be determined in select scenarios (see lower intestinal tract involvement description above)



Upper GI GVHD

If the recipient only has upper GI GVHD during the reporting period, report this as overall grade II. This may differ from prior instructions regarding how to report upper GI GVHD.

Acute GVHD Grading Scenarios:

- A.** A recipient developed stage 2 skin involvement and elevated liver function tests (LFTs) attributed to acute GVHD; however, there was no total bilirubin manifestation. In this case, overall maximum grade I acute GVHD should be reported since the staging / grading can be determined using the GVHD Grading and Staging table above.
- B.** A recipient developed acute liver GVHD with elevated LFTs (i.e., transaminases) with no total bilirubin manifestation. The progress notes indicate stage 1 (grade II overall) acute GVHD of the liver. In this case, the clinical manifestations do not fit the criteria used in the GVHD Grading and Staging table above; “not applicable” would be the best option to report.
- C.** A recipient developed stage 2 skin involvement, which showed improvement in response to topical steroids. However, the recipient then developed hyperbilirubinemia attributed to stage 1 liver involvement; the skin involvement at that time was stage 1. In this case, grade II would be reported (assuming this was the extent of the recipient’s acute GVHD in the reporting period).
- D.** A recipient developed stage 2 skin involvement which resolved in response to topical steroids. Later in the reporting period, the recipient was diagnosed with mild chronic eye GVHD. Shortly thereafter, they were diagnosed with a stage 3 flare of acute skin GVHD. In this case, grade I would be reported. Do not consider any new or persistent acute GVHD symptoms occurring after the onset of chronic GVHD when completing the acute GVHD section of the form.

Question 55: Date maximum overall grade of acute GVHD

Report the date (YYYY-MM-DD) of maximum acute GVHD involvement, based on clinical grade. If the recipient had multiple instances in which their GVHD reached the same maximum grade, report the earliest date. If “not applicable” was reported for question 54, question 55 must be left blank.

Question 56: Did chronic GVHD develop since the date of last report?

Indicate whether a new clinical diagnosis of chronic GVHD was documented during the reporting period. If chronic GVHD was diagnosed during the reporting period, report “yes” and continue with question 57.

If the recipient had a flare of chronic GVHD occurring after at least a 30 day period of symptom quiescence, report “yes” and continue with question 57. Report “no” if symptoms resolve or become quiescent prior to the date of last report and then flare within 30 days. This should be reported as persistent chronic GVHD which is captured in question 58.

Report “no” if chronic GVHD was not clinically diagnosed – initially or as a flare – in the reporting period; this includes instances where chronic GVHD persists from a prior reporting period without flare in the current reporting period.

Indicate “unknown” if there is no information about the recipient’s GVHD status for the reporting period. This option should be used sparingly and only when no judgment can be made about the presence or absence of GVHD in the reporting period.

Question 57: Date of chronic GVHD diagnosis:

Report the date (YYYY-MM-DD) of clinical diagnosis of chronic GVHD. The clinical diagnosis date may not necessarily be the date the symptoms began (example: the recipient developed shortness of breath one month prior to the clinical diagnosis of pulmonary chronic GVHD). If the clinical diagnosis is documented, but the diagnosis date is unclear, obtain documentation from the primary physician confirming the clinical diagnosis date.

If the recipient developed more than one episode of chronic GVHD in the same reporting period, report the date of onset of the first episode of chronic GVHD.

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 58: Did chronic GVHD persist since the date of last report?

Indicate whether chronic GVHD was clinically diagnosed during a previous reporting period and persisted, with active symptoms, into the present reporting period. Do not report quiescent or inactive chronic GVHD, or a prior history of GVHD. If “yes,” continue with question 62; questions concerning chronic GVHD at the time of diagnosis will be skipped. See question 56 for instructions on reporting a chronic GVHD flare.

If the recipient has no active symptoms during the reporting period, report “no” continue with question 64.

Indicate “unknown” if there is no information about the recipient’s GVHD status for the reporting period. This option should be used sparingly and only when no judgment can be made about the presence or absence of GVHD in the reporting period.

Question 59: Maximum grade of Chronic GVHD (according to best clinical judgement):

Report the maximum chronic GVHD involvement, based on clinical grade, as documented by the recipient’s primary care provider. The intent of this question is to capture the maximum grade based on the best clinical judgment. If the maximum clinical grade is not documented, request documentation from the recipient’s primary care provider.

Indicate “unknown” if there is no information about the recipient’s GVHD status for the reporting period. This option should be used sparingly and only when no judgment can be made about the presence or absence of GVHD in the reporting period.

Organ Scoring of Chronic GVHD

Organ	Score 0	Score 1	Score 2	Score 3
Skin % BSA¹	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
Skin Features	No sclerotic features	N/A	Superficial sclerotic features, but not “hidebound”	Deep sclerotic features; “hidebound;” impaired mobility; ulceration
Mouth	No symptoms	Mild symptoms with disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs with partial limitation of oral intake	Severe symptoms with disease signs with major limitation of oral intake
Eyes	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant drops ≤ 3x/day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant drops > 3x/day or punctal plugs) WITHOUT new vision impairment due to keratoconjunctivitis sicca (KCS)	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to keratoconjunctivitis sicca (KCS)
GI Tract	No symptoms	Symptoms without significant weight loss (< 5%)	Symptoms associated with mild to moderate weight loss (5-15%) within 3 months OR moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss (> 15%) within 3 months, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with

				significant interference with daily living.
Liver	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 x ULN	Elevated total bilirubin but ≤ 3 mg / dL or ALT > 5 x ULN	Elevated total bilirubin > 3 mg / dL
Lungs Symptom Score:	No symptoms	Mild symptoms (SOB after climbing one flight of steps)	Moderate symptoms (SOB after walking on flat ground)	Severe symptoms (SOB at rests; requires O2)
Lungs Lung Score:	FEV1 ≥ 80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤ 39%
Joints and Fascia	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought to be due to fasciitis, moderate decrease of range of motion AND mild to moderate limitation of ADL	Contractures WITH significant decrease of range of motion AND significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
Genital Tract²	No signs	Mild signs and females with or without discomfort on exam	Moderate signs and may have signs of discomfort on exam	Severe signs with or without symptoms
Other Features³	No GVHD	Mild	Moderate	Severe

[NIH Consensus Criteria, 2014](#)

¹ Features to be scored by BSA: Maculopapular rash, lichen planus-like features, sclerotic features, papulosquamous lesions or ichthyosis, keratosis pilaris-like GVHD.

² Scoring is based on severity of the signs instead of symptoms, based on limited available data and the opinions of experts. Female or male genital GVHD is not scored if a practitioner is unable to examine the patient.

³ May include ascites, pericardial effusion, pleural effusion(s), nephrotic syndrome, myasthenia gravis, peripheral neuropathy, polymyositis, weight loss without GI symptoms, eosinophilia > 500/μL, platelets < 100,000/μL, others.

Question 60: Specify if chronic GVHD was limited or extensive:

The grading system for chronic GVHD is divided into two categories: limited and extensive. Definitions are based on Sullivan KM, Blood 1981; 57:267.

Report “limited” if chronic GVHD includes only localized skin involvement and/or liver dysfunction. Report “extensive” if any of the following symptoms are attributed to chronic GVHD:

- Generalized skin involvement and/or liver dysfunction
- Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis
- Involvement of the eye: Schirmer’s test with <5 mm wetting, or
- Involvement of the salivary glands or oral mucosa, or
- Involvement of any other target organ

Question 61: Date of maximum grade of chronic GVHD:

Report the date (YYYY-MM-DD) of maximum chronic GVHD involvement, based on clinical grade. If the recipient had multiple instances in which their GVHD reached the same maximum grade, report the earliest date.

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: Is the recipient still taking systemic steroids? (Do not report steroids for adrenal insufficiency, ≤ 10 mg/day for adults, < 0.1 mg/kg/day for children)



Steroids and Non-Steroid Immunosuppression for GVHD

Questions 62 and 63 will only be completed if the center has reported yes for question 44, 46, 56, or 58. If each of these questions has been answered “no,” questions 62 and 63 will be left blank.



Corticosteroids

Corticosteroids are captured differently depending on whether they are used topically or systemically. Use the following guidelines when determining how to report corticosteroids used to treat acute GVHD:

Topical Creams for Skin: Do not report topical ointments or creams used to treat skin GVHD including corticosteroid creams such as Triamcinolone or Hydrocortisone.

Other Topical Treatments: Certain corticosteroid treatments are inhaled or ingested, but are not absorbed and are therefore considered topical. Examples include beclomethasone and budesonide. Do not consider these medications when answering question 62.

Systemic Treatments: Systemic administration of corticosteroids, including use of prednisone and dexamethasone, should be reported in question 62.

Indicate whether the recipient is still taking immunosuppressive agents to treat or prevent GVHD on the date of contact. Refer to the guidelines included in the question text if the recipient is taking low dose steroids or steroids for adrenal insufficiency.

Indicate “not applicable” in any of the following scenarios:

- The recipient has never received systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) to treat or prevent GVHD.
- This form is being completed for a subsequent HCT and the recipient has never received systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) to treat or prevent GVHD since the start of the preparative regimen for the most recent infusion (or since the date of the most recent infusion if no preparative regimen is given).
- The recipient stopped taking systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) to treat or prevent GVHD in a previous reporting period and did not restart systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) during the current reporting period.

Indicate “unknown” if there is no information to determine if the recipient is still taking systemic steroids. This option should be used sparingly and only when no judgment can be made about the recipient still receiving treatment for GVHD on the date of contact. If the recipient has died prior to the discontinuation of systemic steroids used to treat or prevent acute and / or chronic GVHD, select “yes.”

Question 63: Is the recipient still taking (non-steroid) immunosuppressive agents (including PUVA) for GVHD?



Steroids and Non-Steroid Immunosuppression for GVHD

Questions 62 and 63 will only be completed if the center has reported yes for question 44, 46, 56, or 58. If each of these questions has been answered “no,” questions 62 and 63 will be left blank.

Indicate whether the recipient is still taking non-steroidal immunosuppressive agents (including PUVA) to treat or prevent acute and / or chronic GVHD on the date of contact. Descriptions of many immunosuppressive agents are included below.

If the recipient did not receive non-steroidal immunosuppressive agents to treat or prevent acute and / or chronic GVHD during the reporting period, report “not applicable.”

Indicate “not applicable” in any of the following scenarios:

- The recipient has never received non-steroidal immunosuppressive agents (including PUVA) to treat or prevent GVHD.
- This form is being completed for a subsequent HCT and the recipient has never received non-steroidal immunosuppressive agents (including PUVA) to treat or prevent GVHD since the start of the preparative regimen for the most recent infusion (or since the date of the most recent infusion if no preparative regimen was given).
- The recipient stopped taking non-steroidal immunosuppressive agents (including PUVA) to treat or prevent GVHD in a previous reporting period and did not restart non-steroidal immunosuppressive agents (including PUVA) during the current reporting period.

Indicate “unknown” if there is no information to determine if the recipient is still taking non-steroidal immunosuppressive agents. This option should be used sparingly and only when no judgment can be made about the recipient still receiving treatment for GVHD in the reporting period.

Immunosuppressive Agents:

Aldesleukin (Proleukin): Increases production of several white blood cells including regulatory T-cells. This drug is also known as interleukin-2.

ALG (Anti-Lymphocyte Globulin), ALS (Anti-Lymphocyte Serum), ATG (Anti-Thymocyte Globulin) ATS (Anti-Thymocyte Serum): Serum or gamma globulin preparations containing polyclonal immunoglobulins directed against lymphocytes. These drugs are usually prepared from animals immunized against human lymphocytes. Also report the animal source. If “other” is selected, specify the source.

Azathioprine (Imuran): Azathioprine inhibits purine synthesis. Usually it is used at low doses in combination with other treatments.

Bortezomib (Velcade): A proteasome inhibitor.

Cyclosporine (CSA, Neoral, Sandimmune): Calcineurin inhibitor which decreases cytokine production by T-cells. Usually given for ≥ 3 months.

Cyclophosphamide (Cytoxan): Given in high doses near the date of infusion as single agent prophylaxis.

Extra-corporeal photopheresis (ECP): The recipient's blood is removed from the body, exposes to psoralen and ultraviolet light, and re-infused.

FK 506 (Tacrolimus, Prograf): Inhibits the production of interleukin-2 by T-cells.

FK 506 (Tacrolimus, Prograf): Inhibits the production of interleukin-2 by T-cells.

Hydroxychloroquine (Plaquenil): Hydroxychloroquine inhibits transcription of DNA to RNA and is commonly used as an anti-malarial drug.

Interleukin Inhibitor: Interleukin inhibitors suppress production of white blood cells and are grouped according to their target. Examples of IL-2 inhibitors include daclizumab (Zynbryta) and basiliximab (Simulect). Examples of IL-6 inhibitors include tocilizumab (Actemra) and siltuximab (Sylvant).

In vivo monoclonal antibody: Antibody preparations that are infused in the recipient following HSCT. Specify the antibody used as: anti CD25 (Zenapax, Daclizumab, AntiTAC), alemtuzumab (Campath), entanercept (Enbrel), infliximab (Remicade), and / or rituximab (Rituxan).

In vivo immunotoxin: Antibody preparations linked to a toxin that is infused in the recipient following HCT. Specify the immunotoxin.

Janus Kinase 2 Inhibitors: Suppress function of T-effector cells. Examples: ruxolitinib (Jakafi, Jakavi) and tofacitinib (Xeljanz, Jakvinus).

Methotrexate (MTX) (Amethopterin): Inhibits the metabolism of folic acid. It is most often used with cyclosporine and is usually for a short duration of time.

Mycophenolate mofetil (MMF) (CellCept, Myfortic): Inhibits the de novo pathway used for lymphocyte proliferation and activation.

Pentostatin (Nipent): Inhibits adenosine deaminase, which blocks DNA (and some RNA) synthesis.

Sirolimus (Rapamycin, Rapamune): Inhibits the response to interleukin-2, blocking the activation of T-cells.

Tyrosine Kinase Inhibitor (TKI): Suppress function of tyrosine kinases thereby downregulating the function of many other cellular proteins / processes including fibrosis and inflammation. Examples: imatinib (Gleevec, Glivec), nilotinib (Tasigna), and dasatinib (Sprycel).

UV Therapy: UVA or UVB radiation administered to affected areas of the skin in order to suppress proliferation of cells responsible for GVHD.

PUVA (Psoralen and UVA): Psoralen is applied or taken orally to sensitize the skin, and then the skin is exposed to UVA radiation.

UVB: Broadband- or Narrowband-UVB radiation is applied to the affected areas of the skin.

Q64-153: Toxicities

Question 64: 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 or 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 65. If the recipient did not develop CRS, continue with question 71.

Question 65: Date of diagnosis:

Report the date (YYYY-MM-DD) when the first symptom of CRS was documented by a physician or other health care provider in the progress note or chart.

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: Was therapy given? (for CRS)

Indicate “yes” if the recipient received therapy for CRS and continue with question 67. Indicate “no” if no therapy was given for CRS and continue with question 69.

Question 67-68: Specify therapy given for CRS: (check all that apply)

Check all that apply from the list if given to treat the CRS. If “other therapy “ is selected, specify the therapy in question 68.

Question 69-70: Did cytokine release syndrome resolve?

If the cytokine release syndrome resolved, select “yes” and report the date (YYYY-MM-DD) in question 70.

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 71-72: Neurotoxicity:

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

Indicate “yes” if neurotoxicity occurred and continue with question 72. Indicate “no” if neurotoxicity did not occur or “unknown” if unsure whether neurotoxicity occurred and continue with question 77.

Report the date (YYYY-MM-DD) in question 72 when the first symptom of neurotoxicity was documented by a physician or other health care provider in the progress note or chart.

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 73-74: Specify symptoms of neurotoxicity: (check all that apply)

Select all symptom(s) of neurotoxicity.

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.

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

Hemiparesis or other focal motor deficit: 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.

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.

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

Other symptom: specify in question 74

Question 75-76: Did neurotoxicity resolve?

If the cellular therapy associated neurotoxicity resolved, select “yes” and report the date (YYYY-MM-DD) in question 76. 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.

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 77-78: Hemorrhagic stroke

Hemorrhagic stroke occurs when a weakened blood vessel ruptures. Two types of weakened blood vessels usually cause hemorrhagic stroke: aneurysms and arteriovenous malformations (AVMs).

Report the date (YYYY-MM-DD) in question 78 when the hemorrhagic stroke was documented by a physician or other health care provider in the progress note or chart.

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 79-81: Other toxicity:

If the recipient experienced a toxicity that does fit in a category above, select “yes”.

Report the date (YYYY-MM-DD) in question 80 when the other toxicity was documented by a physician or other health care provider in the progress note or chart, and specify the other toxicity in question 81.

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

Specify if the recipient has developed any of the following since the date of last report:

Question 82-138

Report all symptoms if experienced by the recipient, regardless of cause or explanation. These symptoms will be collected for all recipients whether CRS/neurotoxicity developed or not.

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/arthralgias: Myalgia is pain in a muscle or group of muscles and arthralgia 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 (FiO₂<40%): A lower than normal concentration of oxygen in arterial blood requiring supplemental oxygen of <40% FiO₂

Hypoxia requiring more than minimal supplemental oxygen (FiO₂>40%): A lower than normal concentration of oxygen in arterial blood requiring supplemental oxygen of >40% FiO₂.

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

Grade 4 organ toxicity: As defined by the [CTCAE criteria](#), grade 4 toxicity represents life-threatening consequences and urgent intervention is indicated

If “yes” is reported for a symptom, report the date of diagnosis (YYYY- MM-DD) of each symptom and indicate if the symptom was explained entirely by non-CRS causes (e.g. infection, therapy). The intent is to capture all symptoms experienced by the recipient to determine the significance of each symptom in relation to the cellular therapy infusion.

Specify the maximum lab results since the date of last report

Question 139-141: 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 139. If known, report the value in question 140 and the date (YYYY-MM-DD) the sample was collected in question 141.

Question 142-144: Interferon gamma IFN- γ :

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 142. If known, report the value in question 143 and the date (YYYY-MM-DD) the sample was collected in question 144.

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 145-147: Soluble interleukin-2 receptor α (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 145. If known, report the value in question 146 and the date (YYYY-MM-DD) the sample was collected in question 147.

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 148-150: 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 148. If known, report the value in question 149 and the date (YYYY-MM-DD) the sample was collected in question 150.

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 151-153: C-reactive protein:

C-reactive protein (CRP) is a protein produced by the liver and found in the blood. CRP 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 151. If known, report the value in question 152 and the date (YYYY-MM-DD) the sample was collected in question 153.

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

Q154-157: Functional Status

* Questions 154-157

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

Question 154: 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 156. Indicate “no” if the female recipient was not pregnant at any time during the reporting period.

Question 155: 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 and continue with question 156. Indicate “no” if the male recipient’s partner was not pregnant at any time during the reporting period.

Question 156: 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 157.

Question 157: 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”.