

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 for each reporting period, 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, response to the cellular therapy, relapse, current hematologic findings, development of new malignancies, persistence of the cellular product (product specific), development and severity of toxicities (e.g. cytokine release syndrome, neurotoxicity), infection and fertility information.

The Post-CTED Form must be completed at the following time points post-cellular therapy: 100 days, six months, and annually thereafter. The follow-up reporting schedule is determined by whether the product is 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.

Combined follow up

In scenarios where both HCT and cellular therapy forms are being completed, there are two scenarios where the Cellular Therapy Essential Data Follow-Up (4100) form is completed:

Example 1. Cellular therapy after HCT: completion of this form should be based on the time period in relation to the CT infusion date (i.e. 100 days after the CT infusion date). The visit ID should match between the corresponding Post-HSCT Data (2100) or Post-Transplant Essential Data (2450).

Example 2. HCT after cellular therapy: completion of this form should be based on the time period in relation to the HCT infusion date (i.e. 100 days after the HCT infusion date). The visit ID should match between the corresponding Post-HSCT Data (2100) or Post-Transplant Essential Data (2450).

Duplicate questions between HCT and cellular therapy forms may be disabled on the Post-CTED. A full list of enabled/disabled fields can be found on the “[Subsequent Infusions – Updates to Follow-Up Reporting](#)” section of the Data Management Guide. Illustrations of the combined follow up scenarios can also be found the Guide.

Links to sections of form:

[Q1: Product](#)

[Q2-3: Survival](#)

[Q4-8: Subsequent Cellular Infusions](#)

[Q9-11: Best Response to Cellular Therapy](#)

[Q12-20: Peripheral Blood Count Recovery](#)

[Q21-22: Disease Relapse or Progression](#)

[Q23-33: Current Hematologic Findings](#)

[Q34: New Malignancy, Lymphoproliferative or Myeloproliferative Disease/Disorder](#)

[Q35-59: Persistence of Cells](#)

[Q60-79: Graft vs. Host Disease](#)

[Q80-170: Toxicities](#)

[Q171-175: Infection](#)

[Q176-177: Pregnancy Status](#)

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
5/21/2021	4100: Cellular Therapy Essential Data Follow-Up	Modify	The blue box above questions 21-22 was updated: <i>This section is applicable to malignant diseases only and does not only applies to Letetresgene autoleuvel, other products, or cellular therapies with no product name commercially available products.</i>
5/12/2021	4100: Cellular Therapy Essential Data Follow-Up	Add	Added new example 4 for hypogammaglobulinemia resolution date when testing is not exactly at 3 months.
1/22/2021	4100: Cellular Therapy Essential Data Follow-Up	Modify	Version 6 section of the Forms Instruction Manual released. Version 6 corresponds to revision 6 of the Form 4100.

Last modified: May 21, 2021

Q1: Product

Question 1: Name of Product: (for most recent cell therapy infusion)

The name of the product reported will be auto populated with the value reported on the Pre-Cellular Therapy Essential Data (4000) form. If the cellular therapy product infused is a commercially available or pre-commercial product, this question is used to enable questions related to toxicities and disable questions that do not apply.

Combined follow up

In scenarios where both HCT and cellular therapy forms are being completed, and the recipient has received the HCT after the cellular therapy, the product name should be for the prior cellular therapy product.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q2-3: Survival

Question 2: Date of actual contact with the recipient to determine medical status for this follow-up report:

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

In general, the date of contact closest to the designated time point indicated on the form (e.g. Day+100, 6 months, or annual follow-up visit) should be reported. 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 designated time point.

The guidelines below show an ideal approximate range for reporting each post-cellular therapy time point:

Form	Time Point	Approximate Range
F4100	100 Days	+/- 15 days (Day 85 – 115)
F4100	6 Months	+/- 30 days (Day 150 – 210)
F4100	1 Year	+ 60 days (Day 365 – 425)
F4100	Annual reporting 2+ Years	+/- 30 days (Months 23-25, 35-37, etc.)

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 1/1/18 and is seen regularly until 3/1/18. After that, the recipient was referred home and not seen p(. p(. again until 7/1/18 for a restaging exam and 7/5/18 for a meeting to discuss the results.

What to report:

100 Day Date of Contact: 3/1/18 (Since there was no contact closer to the ideal date of 4/11/18, this date is acceptable)

6 Month Date of Contact: 7/5/18 (note the latest disease assessment would likely be reported as 7/1/18)

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-cellular therapy.*

The recipient had an infusion on 1/1/18 and is seen regularly until 3/1/18. After that, the recipient was referred home and not seen again until 1/1/19 for a restaging exam and 1/4/18 for a meeting to discuss the results.

What to report:

100 Day Date of Contact: 3/1/18 (Since there was no contact closer to the ideal date of 4/11/18, this date is acceptable)

6 Month form: Indicate the recipient is lost to follow-up in FormsNet3

1 Year Date of Contact: 1/4/19 (note the latest disease assessment would likely be reported as 1/1/19)

Additional information:

A date of contact should never be used multiple times for the same recipient's forms.

- For example, 6/1/18 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

If the recipient has a subsequent infusion, report the date of contact as the day before the preparative regimen / systemic therapy begins for the subsequent infusion. If no preparative regimen / systemic therapy is given, report the date of contact as the day before the subsequent infusion. In these cases, actual contact on that day is **not** required, and the day prior to the initiation of the preparative regimen / systemic therapy (or infusion, if no preparative regimen / systemic therapy was given) should be reported. This allows every day to be covered by a reporting period and prevents overlap between infusion events.

Example 3. *The recipient receives a subsequent HCT.*

The recipient had a cellular therapy on 1/1/18 and was seen regularly through the first 100 days. During the 6-month reporting period, the recipient goes on to receive a subsequent HCT.

What to report:

1. **Regulatory requirements specify at least 15 years of follow-up data be collected on recipients of genetically modified cellular therapy products:** The date of contact reported should be the date

prior to the start of the preparative regimen (or infusion, if no preparative regimen was given). Both HCT and cellular therapy forms will be completed simultaneously, but all applicable cellular therapy follow-up forms will be reset to the new event date (i.e., Forms 2450+4100 or Forms 2100+4100). The forms will then have the same event date and due date.

2. Cellular therapy products where regulatory requirements do not specify follow-up reporting:

The date of contact reported should be the date prior to the start of the preparative regimen (or infusion, if no preparative regimen was given). Reporting on the cellular therapy event will end.

Combined follow up

In scenarios where both HCT and cellular therapy forms are being completed, the contact date must match between the Form 2100+4100 or Form 2450+4100.

Example 4. *The recipient receives a subsequent cellular therapy.*

The recipient had a cellular therapy on 2/12/18 and was seen regularly through the first 100 days. During the 6-month reporting period, the recipient goes on to receive a subsequent cellular therapy.

What to report

The date of contact reported will be the date prior to the start of the systemic therapy (e.g., lympho-depleting therapy) for the subsequent infusion (in cases where no systemic therapy is given, it is the day prior to the infusion). Reporting on the first cellular therapy event will end. This is true for both genetically modified and non-genetically modified cellular therapy products.

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).

If the death occurred at an outside location and records of death are not available, the dictated date of death within a physician note may be reported. If the progress notes detailing the circumstances of death are available, request these records. These records are useful for completing required follow-up data fields and the cause of death data fields on this form. If the exact date of death is unknown, please view [General Instructions, General Guidelines for Completing Forms](#) for more information on reporting partial and unknown dates.

Example 5. *The recipient has died before their six month reporting period.*

The recipient had an infusion on 1/1/18 and was seen regularly through the first 100 days. They had restaging exams on 4/4/18 and were seen on 4/8/18, and then died on 5/13/18 in the hospital emergency room.

What to report:

100 Day Date of Contact: 4/8/18 (note the latest disease assessment would likely be reported as 4/4/18)

6 Month Date of Contact: 5/13/18 (though the death does not occur within the ideal approximate range for

6 months)

Example 6. *The recipient has died after their six month time point.*

The recipient had an infusion on 1/1/18 and was seen regularly through the first 100 days. The recipient had restaging exams on 4/22/18 and was seen on 4/23/18. Based on findings in the restaging exam, the recipient was admitted for additional treatment. The disease was found to be refractory on a 6/25/18 restaging exam, and the recipient was discharged to hospice on 7/8/18. The hospital was notified via telephone that the recipient died on 7/16/18.

What to report:

100 Day Date of Contact: 4/23/18 (note the latest disease assessment would likely be reported as 4/22/18)

6 Month Date of Contact: 7/16/18 (note the latest disease assessment would likely be reported as 6/25/18)

Question 3: 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 has died, answers to subsequent questions should reflect the recipient's clinical status between the date of last report and their death. The center must also complete a Recipient Death Data (2900) form.

Combined follow up

In scenarios where both HCT and cellular therapy forms are being completed, the death must be reported on both the HCT and cellular therapy forms. If there are Comprehensive Report forms for the HCT, two Recipient Death Data (2900) forms will come due. You only need to complete one form. Contact CIBMTR Center Support to remove the duplicate.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q4-8: Subsequent Cellular Infusions

Combined follow up

In scenarios where both HCT and cellular therapy forms are being completed, duplicate questions will exist between the Cellular Therapy Essential Data Follow-Up (4100) form and the Post-HCT Data (2100) or Post-Transplant Essential Data (2450) form. To reduce the reporting burden, duplicate questions, including subsequent infusions, on the Cellular Therapy Essential Data (4100) form are disabled and will be answered on the Post-HCT Data (2100) or Post-Transplant Essential Data (2450) form.

Subsequent Cellular Infusions

All additional cellular therapy infusions of the same product given for the same indication per protocol require a separate Cellular Therapy Infusion (4006) form. However, they will only require a single Cellular Therapy Product (4003) form for this course of cellular therapy. If a cellular therapy was administered for a different indication (i.e. in response to disease progression / no response, another infusion of a commercial product, etc.) a new Pre-Cellular Therapy Essential Data (4000) form must be completed.

Question 4: Has the recipient received a new course of cellular therapy (unplanned) since the date of the last report?

A course of cellular therapy is all infusions given for the same indication per protocol. If the recipient started a new course of cellular therapy (unplanned) that is different than the course this follow up form is being completed, select **Yes**.

If additional infusions were given for the same indication per protocol, do not report those infusions here. Update the Cellular Therapy Product (4003) form for the applicable product with the correct number of infusions given per protocol. Each infusion requires a separate Cellular Therapy Infusion (4006) form.

In cases where a new course of cellular therapy is being given post-HCT, only the first infusion is reported on the appropriate HCT follow up form (either the Post-HCT Data (2100) or Post-Transplant Essential Data (2450) form). Remaining infusions of a single course of cellular therapy (e.g. multiple DCI/DLIs) are not reported as subsequent infusions. They are captured on a single Cellular Therapy Product (4003) Form as the number of planned infusions.

Example 1. The new course of cellular therapy (post-HCT) consisting of multiple infusions started at the end of the 6- month HCT reporting period and continued into the beginning of the 1-year HCT reporting period.

How to report: The new course of cellular therapy should be reported only on the 6-month HCT follow-up form (either the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450) form) and not on the Cellular Therapy Essential Data Follow-Up (4100) form.

- Reporting an infusion on the Cellular Therapy Essential Data Follow-Up (4100) form as a subsequent

infusion will generate a new Pre-Cellular Therapy Essential Data (4000) form. If you need help removing a Pre-Cellular Therapy Essential Data (4000) form, please make sure the field is corrected and contact CIBMTR Center Support to remove the form.

Example 2. Two non-genetically modified courses of post-HCT cell therapy (e.g., DCI/DLI and MSCs) are given within 100 days of each other in the same reporting period.

How to report: Report the first course as a subsequent cellular therapy on either the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450) form. This will make a new Pre-Cellular Therapy Essential Data (4000) form due. When it is completed, report the second course of cellular therapy on the 100-day Cellular Therapy Essential Data Follow-Up (4100) form to generate the second Pre-Cellular Therapy Essential Data (4000) form.

Example 3. Two non-genetically modified courses of post-HCT (e.g., DCI/DLI and MSCs) are given greater than 100 days apart, but still within the same reporting period.

How to report: Report the first course as a subsequent cellular therapy on the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450) form. Then create a new indication form to report the second course, which will make a second Pre-Cellular Therapy Essential Data (4000) form come due.

Example 4. Two genetically modified courses of post-HCT (e.g., Kymriah and Yescarta) are given in the same reporting period.

How to report: Report the first course as a subsequent cellular therapy on the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450) form. This will make a new Pre-Cellular Therapy Essential Data (4000) form due. When it is completed, combined follow up rules will apply and both HCT and cellular therapy forms will be completed. Report the second course of cellular therapy on the 100-day Cellular Therapy Essential Data Follow-Up (4100) form to generate the second Pre-Cellular Therapy Essential Data (4000) form.

Question 5: Specify the reason for which cellular therapy was given:

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**, continue with question 6 to report the event date.

Question 6: 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 Pre-Cellular Therapy Essential Data (4000) form.

Questions 7 – 8: 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, select Yes and report the date (YYYY-MM-

DD) of the HCT in question 8; also complete the Pre-Transplant Essential Data (2400) form.

Combined follow up

Regulatory requirements specify at least 15 years of follow-up data be collected on recipients of genetically modified cellular therapy products, reporting on the cellular therapy event will continue. Both HCT and cellular therapy forms will be completed.

If the recipient did not receive an HCT since the date of the last report, report **No** and continue with question 9.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q9-11: Best Response to Cellular Therapy

This section may not fit perfectly to all possible indications for cellular therapy. Please select the response that is most applicable to the indication for treatment.

* If the primary disease reported is Acute Lymphoblastic Leukemia (ALL), Chronic Lymphocytic Leukemia (CLL), Hodgkin Lymphoma (HL), Non-Hodgkin Lymphoma (NHL), or Multiple Myeloma (MM) best response is not reported on this form. It will be captured on the corresponding disease form. The question should be left blank and override the error with the override code “Verified Correct (VC)” at this time.

* If the indication for this course of cellular therapy does not require the completion of disease-specific forms, please refer to the disease-specific manuals to locate the response criteria that should be used when reporting best response.

Question 9: What was the best response to the cellular therapy?

This section collects the data known as “best response to cellular therapy”. **The purpose of this section is to report the recipient’s best response to the planned course of cellular therapy.** This section applies to both malignant and non-malignant diseases and disorders. If the recipient received a prior HCT, do not report the response to the HCT, a separate evaluation to establish best response after the cellular therapy is required.

Combined follow up

If the recipient receives a subsequent HCT, do not report the best response to the HCT here. The reported best response to the cellular therapy was previously reported and can no longer be evaluated once a recipient has a subsequent HCT.

For malignant diseases (including solid tumors), appropriate responses are:

- Continued complete response
- Complete response
- Partial response
- No response
- Disease progression

For non-malignant disorders and cardiovascular, musculoskeletal, neurologic, ocular or pulmonary disease, appropriate responses are:

- Normalization of organ function
- Partial normalization of organ function

- No response
- Worsening of organ function

If the indication is infection, the appropriate responses are:

- Complete response
- Partial response
- No response

Table 1. Examples of best response to cellular therapy.

Indication	Applicable response options	Partial Response	Complete Response
GVHD prophylaxis (with HCT)	Do not answer best response	-	-
Prevent disease relapse	Do not answer best response	-	-
Infection prophylaxis	Do not answer best response	-	-
Suboptimal donor chimerism (post-HCT)	Complete Response, Partial Response, or No Response	Increase in chimerism but not 100% donor	100% donor chimerism
Immune Reconstitution (post-HCT)	Complete Response or No Response	-	CD3 >200/mm ³
GVHD treatment (post-HCT)	Complete Response, Partial Response, or No Response	Improvement but not resolution of symptoms, Remains on immune suppression	Improvement but not resolution of symptoms, or Remains on immune suppression
Malignant Hematologic Disorder	Complete Response, Partial Response, Progression, or No Response	Refer to the response criteria as published in the disease specific manual	Refer to the response criteria as published in the disease specific manual
Non-Malignant Disorder	Complete Response, Partial Response, or No Response	Persistent Disease	Resolution of Disease Process
Solid Tumor	Complete Response, Partial Response, No Response, or Disease Progression	Improvement in disease burden, but with persistent disease	No evidence of disease
Cardiovascular Disease, Musculoskeletal Disorder, Neurologic Disease, Ocular Disease, Pulmonary Disease	Do not answer best response	= . -	= . -
Infection treatment	Complete Response, Partial Response, No	Decrease in infectious burden without	Undetectable infection

	Response, or Unknown	resolution	
Other	Do not answer best response	-	-

If the recipient relapses / progresses post-infusion 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 10-11: Was the date of best response previously reported?

If the date of best response was previously reported, select Yes and continue with question 12. **This option is not applicable on the 100 day report.**

Combined follow up

If the recipient receives an HCT after a cellular therapy and the best response to the cellular therapy was previously reported, it can no longer be evaluated once a recipient has a subsequent HCT. It is appropriate to report **Yes** for this scenario 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 11. The date of best response should be the first date all criteria were met.

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

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q12-20: Peripheral Blood Count Recovery

! Questions 12 – 15 can only be completed on the 100 day and 6 month follow-up forms. These questions will be disabled for all subsequent reporting periods.

Combined follow up

In scenarios where an HCT was given after a cellular therapy and this form is now being completed based on the subsequent HCT date, these questions do not apply and are disabled.

Example 1. Cellular therapy after HCT: completion of this form should be based on the time period in relation to the CT infusion date (i.e. 100 days after the CT infusion date). The visit ID should match between the corresponding Post-HSCT Data (2100) or Post-Transplant Essential Data (2450).

Example 2. HCT after cellular therapy: completion of this form should be based on the time period in relation to the HCT infusion date (i.e. 100 days after the HCT infusion date). The visit ID should match between the corresponding Post-HSCT Data (2100) or Post-Transplant Essential Data (2450).

The reporting of peripheral blood count recoveries on the Cellular Therapy Essential Data Follow-Up (4100) form has a different intent than the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450). Systemic therapy (such as lymphodepleting therapy given prior to a CAR-T infusion) may negatively impact ANC and platelet counts. The intent of the questions on the Cellular Therapy Essential Data Follow-Up (4100) form is to determine cell count recovery post systemic therapy, not as a measure of engraftment. These questions are not applicable to all cellular therapies. Not all types of cellular therapies require a course of systemic therapy prior to the infusion.

Absolute neutrophil recovery (ANC) recovery is defined as an ANC of $\geq 500/\text{mm}^3$ (or $\geq 0.5 \times 10^9/\text{L}$) for three consecutive laboratory values obtained on different days. Date of ANC recovery is the date of the first of three consecutive laboratory values where the ANC is $\geq 500/\text{mm}^3$. At some institutions, the laboratory reports display the ANC value once there are sufficient white blood cells to perform a differential count. At other institutions, the laboratory reports do not display the ANC, and it must be calculated from the white blood cell count (WBC). The percent neutrophils (if the differential was performed on an instrument, will include both segmented and band neutrophils. If the laboratory report displays an automated ANC value of exactly $500/\text{mm}^3$, the actual ANC value should be calculated from the manual differential if available. The calculated value from the manual differential will determine ANC recovery. If your institution's laboratory reports do not display the ANC value, use the following calculation to determine the ANC:

Example 3: Calculating Absolute Neutrophil Count (ANC)

%	segmented neutrophils
+	% band neutrophils
=	% neutrophils
x	white blood cell count/mm ³
=	absolute neutrophil count/mm ³
Example:	
(Divide percentage by 100 to convert to decimal)	
	0.45 segmented neutrophils
+	0.05 band neutrophils
=	0.50 neutrophils
x	1000/mm ³ white blood cell count
=	500/mm ³ absolute neutrophil count
ANC 500/mm³ = 0.5 x 10⁹/L = 0.5 x 10⁹/mL = 0.5 x 10³/mm³	

Traditionally, the definition of ANC recovery required the selection of the first date of three consecutive days in which the recipient's ANC was $\geq 0.5 \times 10^9/L$ (500/mm³). For various reasons it may not be possible to obtain daily laboratory values. Under those circumstances, report ANC recovery based upon three consecutive laboratory values (drawn more than a day apart) as long as the ANC remains $\geq 0.5 \times 10^9/L$ (500/mm³).

Tracking the date of ANC recovery may not always be straightforward. In some cases, the ANC may fluctuate for a period of time before the recipient fully recovers. In other cases, the ANC may remain above $\geq 500/mm^3$ for several days immediately post-HCT and then fall below $\geq 500/mm^3$. Do not begin counting ANC values of $\geq 500/mm^3$ towards recovery until the ANC has dropped to the lowest level (nadir) post- infusion. See the following example for more information regarding tracking the date of ANC recovery.

To report dates in this question, use the first of 3 consecutive laboratory values obtained on different days.

Example 4: Tracking ANC Recovery

Infusion Date = May 6

Contact Date = August 15

Date	WBC	%Neutrophils	ANC	
May 7	900	0.6	540	
May 8	850	0.59	502	
May 9	720	0.7	504	
May 10	300	0.45	135	

May 11	15	No differential	—	
May 12	30	No differential	—	
May 13	50	No differential	—	
May 14	250	0.4	100	
May 15	800	0.7	560	<i>Date of initial recovery: ANC \geq 500/mm³ (report this date in question 15)</i>
May 16	1050	0.8	840	
May 17	1000	0.7	700	
May 18	1800	0.6	1080	
May 19	2000	0.55	1100	
May 20	2500	0.53	1325	
May 21-August 14	—	—	—	ANC \geq 500/mm ³ for timeframe
August 15 (contact date)	2250	0.43	968	

Example 5: Initial Recovery with Subsequent Decline and Recovery

Transplant Date = May 6

Contact Date = August 15

Date	WBC	%Neutrophils	ANC	
May 7	900	0.6	540	
May 8	850	0.59	502	
May 9	720	0.7	504	
May 10	300	0.45	135	
May 11	15	No differential	—	
May 12	30	No differential	—	
May 13	50	No differential	—	
May 14	250	0.4	100	
May 15	800	0.7	560	<i>Date of initial recovery: ANC \geq 500/mm³ (report this date in question 13)</i>
May 16	1050	0.8	840	
May 17	1000	0.7	700	
May 18	1800	0.6	1080	
May 19	2000	0.55	1100	
May 20	2500	0.53	1325	

May 21	2250	0.43	968	
May 22	1500	0.45	675	
May 23	800	0.6	480	Date of first decline: ANC \leq 500/mm ³ (report this date in question 15)
May 24	850	0.41	349	
May 25	720	0.53	382	
May 26	500	0.45	225	
May 27	490	0.3	147	
May 28	650	0.7	455	
May 29	800	0.8	640	Date of recovery: ANC \geq 500/mm ³ (report this date in question 18)
May 30-August 14	—	—	—	ANC \geq 500/mm ³ for timeframe
August 15 (contact date)	2245	0.72	1616	

Question 12: Was there evidence of initial recovery?

This question is not applicable to all cellular therapies. Some cellular therapies require a course of systemic therapy prior to the infusion, such as in the case of chimeric antigen receptor (CAR) T-cells. One of the described toxicities is the inability for hematologic recovery, either by an added cycle of chemotherapy in a recipient who received many prior lines of chemotherapy or by a direct toxicity from the cellular therapy.

Indicate whether or not there was evidence of **initial** ANC recovery following this infusion.

Check only **one** response:

- If **Yes**, continue with question 13
- If **No**, continue with question 14
- Report **Not applicable**, if the recipient's ANC never dropped below 500/mm³ (or $\geq 0.5 \times 10^9/L$) at any time post- cellular therapy infusion or the recipient did not receive lymphodepleting therapy. This option is only applicable in the 100 day reporting period. Continue with question 14.



Report Not applicable for DCI / DLI infusions where systemic therapy was not given pre-infusion.

- Report **Previously reported** if this is the 6 month or annual follow-up, and ANC initial recovery (including **Not applicable**) has already been reported on a previous form. Continue with question 14.

Combined follow up

If the recipient receives an HCT after a cellular therapy, and both HCT and cellular therapy forms are being

completed, select **Previously reported** on all Cellular Therapy Essential Data Follow-Up (4100) forms. Peripheral blood count recoveries will now be captured in the context of engraftment on the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450).

Question 13: Date ANC >500/mm³ (first of 3 lab values):

Enter the first date of the three consecutive laboratory values obtained on different days where the ANC was $\geq 500/\text{mm}^3$ (or $\geq 0.5 \times 10^9/\text{L}$). For an example of tracking ANC, see Example 4 above.

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

Question 14: Following the initial recovery, was there subsequent decline in ANC to < 500/mm³ for ≥ 3 days since the date of last report?

Report if there was subsequent decline in ANC $< 500/\text{mm}^3$ (or $< 0.5 \times 10^9/\text{L}$) (three consecutive laboratory values obtained on different days where the ANC declined to $< 500/\text{mm}^3$). If “yes,” continue with question 15. If “no,” continue with question 19.



Multiple Recoveries and Declines

The form does not allow for multiple recoveries and declines in the same reporting period. If the recipient’s ANC initially recovers and then declines, followed by another recovery and another decline, report the date of the first (initial) recovery (question 13), the first decline (question 15), and the last recovery (question 18).

Question 15: Date of decline in ANC to < 500/mm³ for ≥ 3 days (first of 3 days that the ANC declined):

Enter the **first** date of the three consecutive laboratory values obtained on different days where the ANC declined to $< 500/\text{mm}^3$ (or $< 0.5 \times 10^9/\text{L}$). For an example of tracking a subsequent decline and recovery, see Example 5 above.

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

Question 16: Did recipient recover and maintain ANC $\geq 500/\text{mm}^3$ following the decline?

Indicate whether there was evidence of ANC recovery following the decline (three consecutive laboratory values obtained on different days where the ANC was $\geq 500/\text{mm}^3$ (or $\geq 0.5 \times 10^9/\text{L}$). If **Yes**, continue with question 17. If **No**, continue with question 19.

Questions 17- 18: Date of ANC recovery

Report if the date of ANC recovery following the decline is **Known** or **Unknown**. If the date of recovery is **Known**, enter the first date of the three consecutive laboratory values obtained on different days where the

ANC recovered to $\geq 500/\text{mm}^3$ (or $\geq 0.5 \times 10^9/\text{L}$) following the decline. For an example of tracking a subsequent decline and recovery, see Example 5 above. If the date of recovery following decline is **Unknown**, continue with question 19.

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

Question 19: Was an initial platelet count $> 20 \times 10^9/\text{L}$ achieved?

This question does not apply to all cellular therapies. Some cellular therapies require a course of systemic therapy prior to the infusion, such as in the case of chimeric antigen receptor (CAR) T-cells. One of the described toxicities is the inability for hematologic recovery, either by an added cycle of chemotherapy in a recipient who received many prior lines of chemotherapy or by a direct toxicity from the cellular therapy.

The following questions refer to initial platelet recovery following the cellular therapy infusion for which this form is being completed. All dates should reflect **no platelet transfusions administered in the previous seven days**. Report the date of the first of three consecutive laboratory values $\geq 20 \times 10^9/\text{L}$ obtained on different days, as shown in Example 6 below. Note that platelet recovery may take place well after the recipient has returned to the referring physician for care. It is essential that information and laboratory values be obtained from the referring physician.

Transfusions temporarily increase platelet counts. When the data is later used for analysis, it is important to be able to distinguish between a recipient whose body was creating the platelets on its own and a recipient who required transfusions to support the counts.

The following example illustrates the procedure to follow for reporting platelet recovery.

Example 6. Reporting Platelet Recovery

	Transfusion ↓										
Day	0	1	2	3	4	5	6	7	8	9	10
Platelet Count	10,000	35,000	30,000	25,000	10,000	15,000	19,000	23,000	25,000	40,000	50,000
Date	1/1/2008	1/2/2008	1/3/2008	1/4/2008	1/5/2008	1/6/2008	1/7/2008	1/8/2008	1/9/2008	1/10/2008	1/11/2008
								↑ 1st of 3			
Report 1/8/08 as date platelet count $\geq 20 \times 10^9/\text{L}$											

This question relates to **initial** platelet recovery. Dates should not reflect transfusions that took place 7 days prior to the date that it listed. To report dates in this question, use the first of 3 consecutive laboratory values obtained on different days.

Indicate whether or not there was evidence of initial platelet recovery following this cellular therapy

infusion. Check only one response:

- If **Yes**, continue with question 20.
- If **No**, continue with question 21.
- Report **Not applicable**, if the recipient's platelets never dropped below $20 \times 10^9/L$ at any time post-cellular therapy infusion and a platelet transfusion was never required at time post-cellular therapy infusion or the recipient did not receive lymphodepleting therapy. If the recipient's platelet count drops below $20 \times 10^9/L$ and/or the recipient received a platelet transfusion even once, do not report **Not applicable**. This option is only applicable in the 100-day reporting period. Continue with question 21.



Report **Not applicable** for DCI/DLI infusions where systemic therapy was not given pre-infusion.

- Report **Previously reported** if this is the 6 month or annual follow-up, and initial platelet recovery (including **Not applicable**) has already been reported on a previous form. Continue with question 21.

Combined follow up

If the recipient receives an HCT after a cellular therapy, and both HCT and cellular therapy forms are being completed, select **Previously reported** on all Cellular Therapy Essential Data Follow-Up (4100) forms. Peripheral blood count recoveries will now be captured in the context of engraftment on the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450).

Question 20: Date platelets $> 20 \times 10^9/L$:

Enter the first date of three consecutive laboratory values obtained on different days where the platelet count was $\geq 20 \times 10^9/L$. Ensure that no platelet transfusions were administered for seven days immediately preceding this date. Include day seven, as shown in Example 6 above, when determining the recovery date. If three laboratory values were not obtained on consecutive days, but a sequential rise of $\geq 20 \times 10^9/L$ is demonstrated, follow the examples below when determining an estimated date.

Reporting Scenarios:

A. The recipient is being seen in the outpatient clinic and receives a platelet transfusion on January 1. The

platelet count is $22 \times 10^9/L$ on January 2, $24 \times 10^9/L$ on January 3, and $28 \times 10^9/L$ on January 4. The recipient does not come into the clinic for evaluation until one month later. The recipient has not received any more platelet transfusions and the platelet count is well above $20 \times 10^9/L$. Report January 8 (day seven post-platelet transfusion) for the date of platelet recovery.

B. The recipient is being seen in the outpatient clinic and receives a platelet transfusion on January 1. The platelet count is $\geq 20 \times 10^9/L$ on January 2, January 3, and January 4. The recipient is then

discharged back to their primary care physician. The transplant center receives a follow-up note from the primary care physician that states “recipient recovered their platelets in January of 2011.” Report an estimated date of recovery using the guidelines available in [General Instructions, General Guidelines for Completing Forms](#).

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q21-22: Disease Relapse or Progression

* This section is applicable to malignant diseases only and only applies to Letetresgene autoleucel, other products, or cellular therapies with no product name.

Question 21-22: 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. Report **Yes** if disease relapse or progression was detected by any one of the methods in the current reporting period and report the first date (YYYY-MM-DD) of the relapse or progression detected.

If a disease relapse or progression was not detected in the current reporting period, report **No** and continue with question 23.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
Q21 – 22	5/21/ 2021	Modify	The blue box above questions 21-22 was updated: <i>This section is applicable to malignant diseases only and does not only applies to Letetresgene autoleucel, other products, or cellular therapies with no product name commercially available products.</i>	Change made due to update in form validation

Last modified: May 21, 2021

Q23-33: Current Hematologic Findings



Questions 23-33 can only be completed on the 100 day, 6 month, 1 year, and 2 year follow-up forms. These questions will be disabled for all subsequent reporting periods.

Question 23: Date of most recent complete blood count (CBC) sample drawn:

These questions are intended to determine the clinical status of the recipient at time of follow-up for this reporting period post cellular therapy. Testing may be performed multiple times post-infusion; report the most *recent* CBC obtained.

Questions 24-32: Complete blood count results available: (check all that apply)

For each cell type listed, checking the box will indicate a result is available. Provide the most recent laboratory values from the CBC on the date reported in the prior question.

WBC: The white blood cell count is a value that represents all the white blood cells in the blood. If the count is too high or too low, the ability to fight infection may be impaired. Report the WBC value in question 25.

Neutrophils: Neutrophils are a subtype of white blood cell that fights infection. The value on the laboratory report may be a percentage or an absolute value. If an absolute value is reported, divide it by the white blood cell count for a percentage. Neutrophils are also known as polymorphonuclear leukocytes (PMNs). Report the neutrophil value in question 26.

Lymphocytes: Lymphocytes are another subtype of white blood cell that fights infection. The value on the laboratory report may be a percentage of an absolute value. If an absolute value is reported, divide it by the white blood cell count for a percentage. Report the lymphocyte value in question 27.

Hemoglobin: Hemoglobin is a molecule in red blood cells that delivers oxygen to tissues throughout the body. A low hemoglobin count is considered “anemia” and blood transfusions, or growth factors may be required to increase the hemoglobin level. Report the hemoglobin value in question 28.

Hematocrit: The hematocrit is the percentage (sometimes displayed as a proportion) of red blood cells relative to the total blood volume. A low hematocrit may require red blood cell transfusions or growth factors. Indicate if the recipient received a red blood cell transfusion within 30 days prior to sample draw date. Report the hematocrit value in question 29.

If a hematocrit value is reported, also indicate if the recipient received a red blood cell transfusion within 30 days prior to the date of the CBC reported in question 30.

Platelets: Platelets are formed elements within the blood that help with coagulation. A low platelet count, called thrombocytopenia, may lead to easy bleeding or bruising. Thrombocytopenia may require platelet

transfusions. Indicate if the recipient received a platelet transfusion within 7 days prior to testing. Report the platelet value in question 31.

If a platelet value is reported, also indicate if the recipient received a platelet transfusion within 7 days prior to the date of the CBC reported in question 23.

Questions 33: Did the recipient receive any growth factors <7 days before the date the sample was drawn?

Indicate if the recipient received any growth factor (e.g., GCS-F) within 7 days prior to the date the CBC sample was drawn. In the event of a long acting growth factor (e.g., pegfilgrastim (Neulasta®)), please answer this question as **yes** if the recipient received it within 14 days prior to the date the CBC sample was drawn.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
.

Last modified: Jan 22, 2021

Q34: 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. New malignancy related questions will now be asked on the Subsequent Neoplasm (3500) form.

Question 34: 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 **Yes** or **No** if a new or second primary malignancy, including lymphoproliferative disorder, or myeloproliferative disorder, developed in the current reporting period. 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, myelodysplastic and myeloproliferative disorders include but are not limited to:

- Skin cancers (basal, squamous, melanoma)
- New leukemia
- New myelodysplasia
- Solid tumors
- PTLTD (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)

If a new malignancy is reported, please complete the Subsequent Neoplasms (3500) form to answer questions specific to the new malignancy. The option of '**Previously reported**' should only be used if the same malignancy has already been reported on a Subsequent Neoplasms (3500) form that was made due on demand. See examples below. If it is unclear whether or not to use of this option, contact CIBMTR Center Support if there are questions.

Example 1. Recipient develops a new malignancy at day +68. It is reported at the time the 100-day Cellular Therapy Essential Data Follow-Up (4100) form is completed. Question 34 should be answered as 'yes' and the Subsequent Neoplasms (3500) form should be completed to report all new malignancy information.

Example 2. Recipient received a commercial CAR-T product and develops a new malignancy at day +68. Per protocol, the new malignancy should be reported at the time of knowledge of the new malignancy. The Subsequent Neoplasms (3500) form should be created as an unscheduled form in FormsNet3 and completed in a timely manner. In this example, no other new malignancy develops during the 100-day reporting period. When the 100-day Cellular Therapy Essential Data Follow-Up (4100) form is completed, question 34 should be answered as '**previously reported**'.

Example 3. Recipient received a commercial CAR-T product and develops a new malignancy at day +68. Per protocol, the new malignancy should be reported at the time of knowledge of the new malignancy. The Subsequent Neoplasms (3500) form should be created as an unscheduled form in FormsNet3 and completed in a timely manner. Another new malignancy develops at day +100 after the same CAR-T infusion. It is decided to report the 2nd new malignancy on the 100-day Cellular Therapy Essential Data Follow-Up (4100) form since it is due at the same time. Question 34 should be answered as '**yes**' to create a second Subsequent Neoplasms (3500) form.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q35-59: Persistence of Cells

! This section pertains to the evaluation of persistence of a cellular product in the recipient and only applies to genetically-modified cellular therapy products.

Question 35: 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 in the current reporting period, select **Yes**.

If tests were not performed to detect persistence of the cellular therapy product in the current reporting period, select **No** and continue with question 60.

Question 36: 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 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 **Yes** or **No** whether molecular assay testing was performed to detect the persistence of the genetically modified cellular therapy product within the reporting period. If persistence was not evaluated by molecular assay, report **No** and continue with question 41.

Question 37: 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 date of the first negative test result
- there were positive and negative results, report the date of the last positive test (do not report negative results)

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

Questions 38-39: Specify the cell source: (check all that apply)

Specify the cell source of the sample collected for evaluation by molecular assay. Select all that apply. If multiple cell sources were used and persistence was detected in some but not all the samples, report **ONLY** the cell sources that were positive. If **Other source** is selected, specify the source in question 39.

Question 40: Were the infused cells detected?

Indicate **Yes** or **No** if the infused cells were detected by molecular assay.

Question 41: 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. The nature of flow cytometry is to detect cells based on a specific probe. To report flow cytometry results, the test must have been performed to specifically detect the genetically modified cellular therapy product.

Indicate **Yes** or **No** if flow cytometry testing was performed to detect the persistence of the genetically modified cellular therapy product within the reporting period. If flow cytometry was not performed, select **No** and continue with question 49.

Question 42: 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 date of the first negative test result
- there were positive and negative results, report the date of the last positive test (do not report negative results)

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 43-44: Specify the cell source (check all that apply)

Specify the cell source of the sample collected for evaluation by flow cytometry. Select all that apply. If multiple cell sources were used and persistence was detected in some but not all the samples, report **ONLY** the cell sources that were positive. If **Other source** is selected, specify the source in question 44.

Question 45: Were the infused cells detected?

Indicate **Yes** or **No** if the infused cells were detected by flow cytometry testing (immunophenotyping).

Question 46: Were B-cell counts monitored after infusion?

CAR-T cells that target antigens (CD19, CD20, CD22, BCMA) on B-cells do not distinguish between

cancerous and normal B-cells. As result, the recipient can develop B-cell aplasia (low number or absence of B-cells). B-cell aplasia can be used as a surrogate to track persistence of the product. If the recipient has B-cell aplasia, then the product may still be present.

Indicate **Yes** or **No** if B-cell counts were monitored during the current reporting period. If B-cell counts were not monitored, select **No** and continue with question 49.

Question 47: Was there B-cell recovery?

A guideline for B-cell aplasia is a B-cell count of $<50 \text{ cells}/\mu\text{L}$, select Yes. If B-cells never recovered, report No and continue with question 49.

B-cell counts in the blood do vary with age, and children have much higher counts than adults. The younger the child, the higher is the concentration.

Question 48: Date of B-cell recovery

Report the date (YYYY-MM-DD) the flow cytometry report showed B-cell recovery.

Question 49: 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 **Yes** or **No** if immunohistochemistry testing was performed to detect the persistence of the genetically modified cellular product within the reporting period. If immunohistochemistry testing was not performed in the current reporting period, report **No** and continue with question 54.

Question 50: 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 date of the first negative test result
- there were positive and negative results, report the date of the last positive test (do not report negative results)

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 51-52: Specify the cell source:

Specify the cell source of the sample collected for evaluation by immunohistochemistry. Select all that apply. If multiple cell sources were used and persistence was detected in some but not all the samples,

report **ONLY** the cell sources that were positive. If **Other source** is selected, specify the source in question 52.

Question 53: Were the infused cells detected?

Indicate **Yes** or **No** if the infused cells were detected by immunohistochemistry testing.

Questions 54-55: Was persistence evaluated by other method?

Indicate **Yes** or **No** if persistence of cells was tested by a method not listed above. If **Yes**, specify the other method used to evaluate persistence of cells in question 55. If persistence of cells was not tested by another method, select **No** and continue with question 60.

Question 56: 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 date of the first negative test result
- there were positive and negative results, report the date of the last positive test (do not report negative results)

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 57-58: Specify the cell source:

Specify the cell source of the sample collected for evaluation by other method. Select all that apply. If multiple cell sources were used and persistence was detected in some but not all the samples, report **ONLY** the cell sources that were positive. If Other source is selected, specify the source in question 58.

Question 59: Were the infused cells detected?

Indicate **Yes** or **No** if the infused cells were detected by other method.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Apr 29, 2021

Q60-79: Graft vs. Host Disease

* Autologous Infusions

Questions 60-77 should be completed for allogeneic infusions only. If this was an autologous infusion, continue to the "Toxicities" section.

Combined follow up

In scenarios where both HCT and cellular therapy forms are being completed, there are duplicate questions across the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450) forms and the Cellular Therapy Essential Data Follow-Up (4100) form. To reduce the reporting burden, duplicate questions, including GVHD, on the Cellular Therapy forms are disabled and will be answered on the Post-HSCT Data (2100) or Post-Transplant Essential Data (2450) form.

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 infusion, 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 60-71). 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 of the form (questions 72-77). If chronic GVHD was diagnosed in a prior reporting period, report "no" for questions 60 and 62 in each

subsequent reporting period. See reporting scenarios included in question 60.

Question 60: Did acute GVHD develop since the date of last report?

Questions 60 and 62 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 60 or question 62 must be answered Yes unless there has been a prior / concurrent diagnosis of chronic GVHD (see note above question 60). There will not be a situation where Yes is reported for both question 60 and question 62. If question 60 is answered yes and a diagnosis date has been reported in question 61, question 62 will be disabled in FormsNet3SM. Centers should report Yes for question 60 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 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 60).

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 60 and **Yes** for question 62. Question 62 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 60 and 62.

Report **No** for questions 60 and 62 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 60).

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 60: Report “yes” to indicate a new clinical diagnosis of acute GVHD. Question 61: Report the initial date of diagnosis (2/1/2015).

Question 62: Leave blank. This question will be skipped whenever a diagnosis date has been entered in question 61.

Questions 63-69: Answer these questions based on the assessments performed at the time of diagnosis (2/1/2015).

Six Month Post-TED Form:

Question 60: 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 61: Leave blank. This question will be skipped whenever question 60 is answered “no.”

Question 62: Report “yes” to indicate GVHD persists from a previous report.

Questions 63-69: Leave blank. Answering “yes” for question 62 prevents the center from re-reporting diagnosis information already captured on the 100 day form.

One Year Post-Infusion Data Form:

Question 60: Report “yes” to indicate a flare of acute GVHD occurred at least 30 days after resolving during a prior reporting period.

Question 61: Report the diagnosis date of the flare occurring during the reporting period (8/15/2015).

Question 62: Leave blank. This question will be skipped whenever a diagnosis date has been entered in question 61.

Questions 63-69: 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 product 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 60: Report “yes” to indicate a new clinical diagnosis of acute GVHD.

Question 61: Report the initial date of diagnosis (2/1/2015).

Question 62: Leave blank. This question will be skipped whenever a diagnosis date has been entered in question 61.

Questions 63-69: Answer these questions based on the assessments performed at the time of diagnosis (2/

1/2015).

Six Month Post-Infusion Data Form:

Question 60: Report “no” to indicate acute GVHD did not develop during the reporting period.

Question 61: Leave blank. This question will be skipped whenever question 60 is answered “no.”

Question 62: 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 60 and 62. 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 60.

Question 61: 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 62: Did acute GVHD persist since the date of last report?

Question 62 will only be enabled in FormsNet3 if the center has reported **No** for question 60 and, therefore, has not reported a date of diagnosis in question 61. If prompted to answer question 62, 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 60).

Report **No** for questions 60 and 62 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 60).

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 63: 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
Grade⁵			
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.

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

Question 64-69: 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

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 questions 65-66 “Other site(s) involved with acute GVHD”.

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 69. 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 70: 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 60 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 71: 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 70, question 71 must be left blank.

Question 72: 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 73.

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 73. 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 74.

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 73: 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 74: Did chronic GVHD persist since the date of last report?

Question 74 will only be enabled in FormsNet3 if the center has reported **No** for question 72 and, therefore, has not reported a date of diagnosis in question 73. 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 75; See question 72 for instructions on reporting a chronic GVHD flare.

If the recipient has no active symptoms during the reporting period, report **No** and continue with question 78.

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 75: 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.

Question 76: 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

Note: Schimer's test is required if eye involvement is the only symptom of chronic GVHD. If there are other symptoms of chronic GVHD such as lichen sclerosis of the mouth and skin involvement in addition to the eye symptoms, the Schirmer's test is not required.

Question 77: 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 78: Is the recipient still taking systemic steroids? (Do not report steroids for adrenal insufficiency or a steroid taper of ≤ 10 mg/day for adults, < 0.1 mg/kg/day for children)



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 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 78.

Systemic Treatments: Systemic administration of corticosteroids, including use of prednisone and dexamethasone, should be reported in question 78.

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

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.
- 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.

Examples of 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.

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 HCT. 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.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q80-170: Toxicities

* Report any observed toxicity or infection that occurs post-infusion in this reporting period, regardless of causality and whether or not treatment was administered. The intent is to capture all toxicities diagnosed after the cellular therapy infusion. Although treatment given post-infusion may have the effect of re-activating the product and inducing toxicities (e.g. CRS), these toxicities should still be captured in this section of the form.

Combined follow up

In scenarios where both HCT and cellular therapy forms are being completed, toxicities should still be reported when an HCT follows a cellular therapy. It is possible to have CAR-T cell reactivation post-HCT.

Question 80: Did the recipient experience Cytokine Release Syndrome (CRS)?

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 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 (must be $\geq 100.4\text{F}$ or $\geq 38\text{C}$), 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.

Indicate **Yes** if CRS occurred or persisted into the current reporting period. Indicate **No** if CRS did not occur or persist into the current reporting period and continue with question 110.

Question 81: Was the date of diagnosis previously reported?

If the CRS was diagnosed in a previous reporting period, the symptoms continue into this reporting period, and the date has already been reported, select **Yes** and continue with question 83. If CRS was not diagnosed in a prior reporting period, report **No**.

Question 82: 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.

Questions 83-85: Specify therapy given for CRS: (check all that apply)

Check all that apply from the list of the drug(s) given to treat CRS in this reporting period. If **Other therapy** is selected, specify the therapy in question 84.

If **Tocilizumab** was given to treat the CRS, report the number of doses given in question 85. This information is important in the grading of the CRS event.

Questions 86-96: Indicate symptoms of CRS (check all that apply)

Indicate which symptoms of CRS the recipient experienced in the current reporting period, check all symptoms that apply. For each symptom reported, also report the date of onset. If there were multiple occurrences of a symptom (e.g. fever), report the first occurrence.

If CRS is persisting from a prior reporting period, report the symptoms that worsened or carried over in this reporting period.

Fevers ($\geq 100.4\text{F}$ or $\geq 38\text{C}$): A disorder characterized by elevation of the body's temperature above the upper limit of normal. Do not report fever less than 100.4F or 38C in this field. Fever less than 100.4F or 38C does not qualify as a symptom of CRS. Report the date of fever onset in question 87. If there were multiple fevers in the reporting period, report the first occurrence.

Hypotension requiring therapy: Abnormally low blood pressure requiring treatment with volume resuscitation using intravenous isotonic fluids or vasopressors such as norepinephrine, dopamine, dobutamine, epinephrine, phenylephrine, or vasopressin. The use of vasopressors to control blood pressure is an indirect assessment of severity of CRS. Report the date of hypotension onset in question 88.

Options for number of vasopressors include 1 or >2 and can be used to determine the grade. One important consideration here is the use of vasopressin, which can be used with fluids or other vasopressors to stabilize the blood pressure. In order to assess severity, only patients who received two or more vasopressor agents at the same time excluding vasopressin, should be marked as >2 vasopressors. Addition of vasopressin to other vasopressor agents does not reflect the same level of acuity compared to a patient requiring 2 or more vasopressors without vasopressin. Only use the option of number of vasopressors as >2 for patients who are receiving multiple vasopressors at the same time excluding vasopressin.

Specify any vasopressor(s) used at the same time as a single therapy to treat hypotension in question 92 and 93. And report if hypotension was controlled with therapy in question 94. Controlled means not worsening clinically or resolving the hypotension / managing it without the need for additional agents such as pressors.

Hypoxia requiring minimal supplemental oxygen ($\text{FiO}_2 < 40\%$): A lower than normal concentration of oxygen in arterial blood requiring supplemental oxygen of $<40\%$ FiO_2 . One example here is the delivery of supplemental oxygen with a low-flow nasal cannula or blow-by device. Report the date of onset in question 95.

Hypoxia requiring more than minimal supplemental oxygen ($\text{FiO}_2 > 40\%$): A lower than normal concentration of oxygen in arterial blood requiring supplemental oxygen of $>40\%$ FiO_2 . Also specify if

positive pressure ventilatory support is required, such as CPAP, BiPAP, intubation or mechanical ventilation. Do not report use of CPAP for sleep apnea. Examples here include the requirement of supplemental oxygen delivered through a high-flow nasal cannula, facemask, opti-flow, non-rebreather mask or Venturi mask. Report the date of onset in question 96.

Source: Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Questions 97-98: Was positive pressure ventilatory support required (CPAP, BiPAP, intubation, and mechanical ventilation):

This option outlines the need of devices considered as positive pressure ventilation which could be non-invasive like continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP or BPAP), or invasive, which requires endotracheal intubation with mechanical ventilation.

Patients who use BiPAP or CPAP for obstructive sleep apnea are not considered the same here and should not be reported in this question. The intent of this question is the treatment of respiratory insufficiency or failure.

If positive pressure ventilatory support was required, select Yes and report the start date in question 98. If the recipient required multiple types of positive ventilatory support, report the start date of the first method. If positive pressure ventilatory support was not required, report No and continue with question 99.

Questions 99-100: Were there features related to macrophage activation syndrome (MAS) / hemophagocytic lymphohistiocytosis (HLH)?

Macrophage activation syndrome (MAS) and hemophagocytic lymphohistiocytosis (HLH) are a severe systematic inflammatory syndromes caused by excessive activation and expansion of T lymphocytes and macrophagic histiocytes. MAS/HLH is within the spectrum of CRS. Some patients may present with CRS and progress into this more aggressive syndrome.

Report the date (YYYY-MM-DD) when the first symptom of MAS/HLH was documented by either the date of the pathological confirmation of MAS/HLH (bone marrow or other organ biopsy) or the first date of a ferritin level > 100,000 ng/mL among patients without pathologic confirmation but with high clinical suspicion (persistent high fevers, ongoing cytopenias, high triglyceride levels, low fibrinogen levels or organomegaly)

Questions 101: Did the recipient have splenomegaly?

Indicate if the recipient had splenomegaly (i.e., abnormal enlargement of the spleen) that could be attributed to MAS/HLH. Splenomegaly is often documented during the physician's physical assessment of the recipient and represents an abnormal finding. Splenomegaly can also be detected by imaging techniques such as ultrasonography, CT or MRI.

Questions 102: Was MAS/HLH confirmed by a bone marrow biopsy?

The pathognomonic feature of MAS is a bone marrow examination that reveals numerous well differentiated

macrophages actively phagocytosing hematopoietic cells. MAS is a subset of HLH and a bone marrow aspirate and biopsy may be performed to look for microscopic evidence of hemophagocytosis as part of the diagnostic work-up for HLH.

Report **Yes** if a bone marrow biopsy was obtained to confirm MAS/HLH. Report “no” if a bone marrow biopsy was not obtained to confirm MAS/HLH.

Questions 103-107: Specify the laboratory values collected (check all that apply)

Hypofibrinogenemia and hypertriglyceridemia support the diagnosis of HLH. The laboratory values should be at the time of diagnosis of MAS/HLH.

Report the lowest fibrinogen level in question 104 and the date the sample was collected in question 105.

Report the highest triglyceride level in question 106 and the date the sample was collected in question 107.

Questions 108-109: Did cytokine release syndrome resolve?

If the cytokine release syndrome resolved, select **Yes** and report the resolution date (YYYY-MM-DD).

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

If the cytokine release syndrome did not resolve, select **No** and continue with question 110.

It is possible a patient could experience CRS like symptoms after the CRS event has previously resolved. In these situations, please report the date of onset, the worst grade of both events, and the resolution of the second event if applicable. Please contact CIBMTR Center Support for a review of these types of scenarios.

Questions 110: Did the recipient experience neurotoxicity (ICANS)?

ICANS (Immune effector Cell-associated Neurotoxicity Syndrome) 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** or **No** if neurotoxicity occurred or persisted in the current reporting period. If neurotoxicity did not occur / persist into the current reporting period or it is not known, select **No** or **Unknown**, respectively then continue with question 129.

Questions 111: Was the date of onset previously reported?

If the neurotoxicity was diagnosed in a previous reporting period and symptoms continue into this reporting

period and the date has already been reported, select **Yes** and continue with question 117. If neurotoxicity (ICANS) was not diagnosed in a prior reporting period, report **No** and enter the date of neurotoxicity (ICANS) diagnosis in question 114.

Question 112: Date of neurotoxicity (ICANS) onset:

Report the date (YYYY-MM-DD) when the first symptom of neurotoxicity (ICANS) 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.

Questions 113-114: Specify therapy given for neurotoxicity: (check all that apply)

Check all that apply from the list of drug(s) given to treat neurotoxicity (ICANS) in this reporting period. If **Other therapy** is selected, specify the therapy in question 114.

Question 115: Which cognitive assessment was performed?

The CAR Toxicity (CARTOX) 10-point neurologic assessment assigns one point for each task performed correctly. A score of 10 is normal. These scales assess cognition and the level of encephalopathy more precisely. They include assessments of orientation, naming, writing, and attention with a score associated with each positive answer. Lower scores are associated with a higher level of encephalopathy.

Unresponsive patients score 0 for all scales. Some centers performed these evaluations multiple times a day. These questions attempt to capture the worst score.

The Immune Effector Cell-Associated Encephalopathy (ICE) assessment is a slightly modified version of the CARTOX-10 assessment. It includes an element for command following.

If another assessment was performed, convert to CARTOX or ICE to report here. See question 120 for a conversion of the Cornell Assessment of Pediatric Delirium (CAPD) to CARTOX or ICE.

Question 116: What was the lowest score? (e.g. CARTOX-10, ICE)

Assessment	CARTOX-10 (12)	ICE SCORE (IMMUNE EFFECTOR ENCEPHALOPATHY) ASSESSMENT
Orientation	Orientation to year, month city, hospital, or President/Prime Minister of country of residence: 5 points	Orientation to year, month, city, or hospital: 4 points
Naming	Name 3 objects (e.g., point to clock, pen, button): 3 points	Name 3 objects (e.g., point to clock, pen, button): 3 points
Writing	Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point	Ability to write a standard sentence (e.g., Our national bird is the bald eagle): 1 point
Attention	Count backwards from 100 by 10: 1 point	Count backwards from 100 by 10: 1 point
Following Commands	---	"Show me two fingers," or, "Close your eyes and stick out your tongue.": 1 point

Source: ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation*, Volume 25, Issue 4, April 2019, Pages 625-638

Encephalopathy assessment for children age <12 years using the Cornell Assessment of Pediatric Delirium (CAPD)

A lower CARTOX / ICE score indicates a higher grade of neurotoxicity (symptom/signs)	Grade 1	Grade 2	Grade 3	Grade 4
Neurological assessment score	Mild (7-9)	Moderate (3-6)	Severe (0-2)	Critical/obtunded

When converting CAPD to CARTOX or ICE, report any number in the corresponding range (e.g. CAPD of ≥ 9 , report 0, 1, or 2)

Assessment	CARTOX	ICE	CAPD
Grade 1	7-9	7-9	1-8
Grade 2	3-6	3-6	1-8
Grade 3	0-2	0-2	≥ 9



For symptoms of neurotoxicity (ICANS), report the HIGHEST grade observed in this reporting period.

Questions 117-126: Indicate the symptoms of neurotoxicity (ICANS) (check all that apply)

Aphasia (speech impairment): Note that grade 3 dysphasia is defined as aphasia.

Cerebral edema: A swelling in the brain caused by the presence of excessive fluid. Specify the type of cerebral edema in question 119.

Cerebral vascular accident (stroke): A disorder characterized by a decrease or absence of blood supply to the brain caused by obstruction (thrombosis or embolism) of an artery resulting in neurological damage. Also report the date of onset and the type of 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). Ischemic strokes occur when the arteries to your brain become narrowed or blocked, causing severely reduced blood flow (ischemia). Report the date of onset and type in questions 120 and 121.

Depressed level of consciousness: A disruption in how the brain works that causes a change in behavior. This change can happen suddenly or over days and ranges from increased sleepiness to coma. Specify the most severe level in question 122.

Dysphasia (speech impairment): The loss of ability to understand or express speech, caused by brain damage. Report the grade of dysphasia in question 123.

Hallucinations: A disorder characterized by a false sensory perception in the absence of an external stimulus (visual or other type).

Hemiparesis / paraparesis / other motor deficit: Weakness on one side of the body (hemiplegic, partial paralysis of the lower limbs (legs), or other sudden loss of connectivity between the CNS and muscles.

Leukoencephalopathy: A disorder characterized by diffuse reactive astrocytosis with multiple areas of necrotic foci without inflammation.

Seizure: Uncontrolled electrical activity in the brain, which may produce a physical convulsion, minor physical signs, thought disturbances or a combination of symptoms. Specify the type of seizure and severity (grade) in questions 124-126. Report the worst type of seizure if multiple types were experienced in a single reporting period.

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

Other symptom: If the recipient experienced a symptom of neurotoxicity not listed above, report here and specify the symptom in question 118.

Source: Common Terminology Criteria for Adverse Events (CTCAE) v5.0 and ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation*, Volume 25, Issue 4, April 2019, Pages 625-638

Questions 127-128: Did neurotoxicity resolve?

If the cellular therapy associated neurotoxicity resolved, select **Yes** and report the resolution date (YYYY-MM-DD) in question 127. 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.

Other toxicities

Questions 129: Hypogammaglobulinemia

Hypogammaglobulinemia refers to low levels of circulating gammaglobulins, or immunoglobulins, in the blood and often determined by quantitative levels of immunoglobulins G (IgG), A (IgA) and M (IgM); or most commonly IgG only. Levels lower than 600 mg/dL of circulating IgG are considered to be hypogammaglobulinemia. Normal limits of IgG concentration in the blood vary with age. Children ages 4 to 10, levels lower than 500mg/dL are considered hypogammaglobulinemia. Children younger than four years, as levels of IgG can be much lower and still be within normal ranges for the age, the diagnosis of hypogammaglobulinemia needs to be confirmed with the treating physician.

Hypogammaglobulinemia is common after CAR-T infusions that target CD19+ cells, which produce immunoglobulins. The degree of hypogammaglobulinemia is associated with a higher risk of infection.

Example 1. For an adult recipient, IgG levels were below 600 mg/dL pre-cellular therapy infusion and continue to be low post-infusion. This is reported as a toxicity, even though IgG level were below 600 mg/dL pre-infusion.

Example 2. For an adult recipient, IgG levels were below 600 mg/dL pre-cellular therapy infusion and continues to be low post-infusion and immunoglobulin replacement therapy (IVIG) was given post-infusion. This is reported as a toxicity, even though IgG level were below 600 mg/dL pre-infusion.

Example 3. For an adult recipient, IgG levels were never below 600 mg/dL, but levels were decreasing post-infusion and immunoglobulin replacement therapy (IVIG) was given. This is not reported as a toxicity since the IgG levels were never below 600 mg/dL, even though immunoglobulin replacement therapy was given.

Example 4. For an adult recipient, IVIG was administered prophylactically, but IgG levels were never below 600 mg/dL. This is not reported as a toxicity since the IgG levels were never below 600 mg/dL.

If IgG dropped below 600 (or 500 for children ages 4 – 10) in the reporting period, regardless if the IgG was below 600 prior to infusion, or if the IgG was below 600 (or 500 for children ages 4 – 10) and persistent into the current reporting period, report hypogammaglobulinemia developed or persisted in this reporting period, by selecting **Yes**. If hypogammaglobulinemia did not develop in this reporting period, select **No** and continue with question 136.

Report **Unknown** if the IgG levels were not tested in the reporting period.

Questions 130: Was the date of onset previously reported?

If the hypogammaglobulinemia was diagnosed in a previous reporting period, symptoms continue into this reporting period, and the date has already been reported, select **Yes** and continue with question 136. If hypogammaglobulinemia was not diagnosed in a prior reporting period, report **No** and enter the date of hypogammaglobulinemia diagnosis in question 131.

Questions 131: Date of onset:

Report the date (YYYY-MM-DD) when the hypogammaglobulinemia was documented by either a physician / health care provider or determined by lab results. Immunoglobulin replacement therapy (IVIG) is not required for the diagnosis of hypogammaglobulinemia

Example 1. IgG levels were measures at 450 mg/dL on June 1; however, immunoglobulin replacement therapy (IVIG) was not given and on June 15, IgG levels had dropped to 400, immunoglobulin replacement therapy was given as this time. Report the onset date as June 1.

Example 2. IgG levels were measures at 450 mg/dL on May 15, no immunoglobulin replacement therapy (IVIG). Report the onset date as May 15.

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

Questions 132-133: Did hypogammaglobulinemia resolve?

Hypogammaglobulinemia can be reported as resolved if there are sustained normal levels of IgG in the blood without the need for IVIG infusions for 3 consecutive months.

Example 1. IgG levels were measures at 450 mg/dL on June 1; immunoglobulin replacement therapy (IVIG) was given on June 15. IgG levels were monitored for the next 4 months and no further immunoglobulin replacement therapy (IVIG) was given. IgG levels went above 600 mg/dL on September 15 and continued to rise. Report the resolution date as the first test result that was greater than 600 mg/dL (September 15).

Example 2. IgG levels were measures at 450 mg/dL on May 15, no immunoglobulin replacement therapy (IVIG) is given. IgG levels were monitored and went above 600 mg/dL on June 3 and normal levels were sustained. Report resolution date as the first test result that was greater than 600 mg/dL (June 3).

Example 3. IgG levels were measures at 450 mg/dL on June 1; immunoglobulin replacement therapy (IVIG) was given on June 15. IgG levels were not monitored, and the recipient has returned to their primary oncologist. In the absence of any testing, the resolution date can be reported as the date 3 months after the last IVIG infusion.

Example 4. For an adult recipient, IgG levels were measured at 450 mg/dL on June 1; immunoglobulin replacement therapy (IVIG) was given on June 15. IgG levels were monitored over the next three and a half

months and no further immunoglobulin replacement therapy (IVIG) was given. IgG levels were tested, and measured greater than 600 mg/dL, on August 29 (2.5 months after last IVIG infusion) and September 25 (3.2 months after the last IVIG infusion). The resolution date should be greater than or equal to 3 months after the last IVIG infusion; therefore September 25 should be reported as the resolution date.

If the hypogammaglobulinemia resolved, select **Yes** in question 132 and report the resolution date (YYYY-MM-DD) in question 133 as documented by a physician or other health care provider in the progress note or chart.

Questions 134-135: Did recipient require immunoglobulin replacement therapy?

Replacement therapy is given to prevent infections. If the recipient required immunoglobulin replacement therapy (IVIG) as a result of hypogammaglobulinemia that developed post-infusion, select Yes and indicate if the recipient is still requiring the therapy on the contact date for this reporting period. If the last immunoglobulin replacement therapy (IVIG) was given less than 3 months from the date of contact, report Yes unless it's clearly stated in the medical record that no more immunoglobulin replacement therapy is required.

Questions 136: Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a disorder characterized by metabolic abnormalities that result from a spontaneous or therapy-related cytolysis of tumor cells.

Indicate **Yes** or **No** if tumor lysis syndrome developed in the current reporting period. If tumor lysis syndrome did not develop in this reporting period or it's unknown if tumor lysis syndrome developed, select No or Unknown respectively and continue with question 142.

Questions 137: Was the date of onset previously reported?

If the tumor lysis syndrome was diagnosed in a previous reporting period, symptoms continue into this reporting period, and the date has already been reported, select **Yes** and continue with question 139. If tumor lysis syndrome was not diagnosed in a prior reporting period, report **No** and enter the date of tumor lysis syndrome diagnosis in question 138.

Questions 138: Date of onset:

Report the date (YYYY-MM-DD) when the tumor lysis syndrome 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.

Questions 139: Grade:

Report the most severe grade of the tumor lysis syndrome as documented by a physician or other health

care provider in the progress note or chart.

- **Grade 3:** Present
- **Grade 4:** Life-threatening consequences: urgent intervention indicated
- **Grade 5:** Death

Questions 140-141: Did tumor lysis syndrome resolve?

If the tumor lysis syndrome resolved, select Yes in question 140 and report the resolution date (YYYY-MM-DD) in question 141 as documented by a physician or other health care provider in the progress note or chart.



Reporting multiple other toxicities

FormsNet3 application: Complete questions 143-147 for each other toxicity by adding additional instance(s) in the FormsNet3 application.

Paper form submission: Copy question 143-147 and complete for each other toxicity being reported.

Questions 142-143: Other toxicity:

Other toxicities reported should be related to the cellular therapy infusion that are documented in the medical record as clinically important and relevant and do not fit into another category listed on this form.

If the recipient experienced a toxicity that does not fit in a category above, select Yes and specify the other toxicity in question 143.

Questions 144: Was the date of onset previously reported?

If the other toxicity was diagnosed in a previous reporting period, symptoms continue into this reporting period, and the date has already been reported, select **Yes** and continue with question 146. If the other toxicity being reported was not diagnosed in a prior reporting period, report **No** and enter the date of the other toxicity diagnosis in question 145.

Questions 145: Date of onset:

Report the date (YYYY-MM-DD) when the other toxicity was documented by either a physician / health care provider or determined by lab results.

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

Questions 146-147: Did other toxicity resolve?

Indicate **Yes** or **No** if the other toxicity resolved. If **Yes**, report the resolution date (YYYY-MM-DD) question 147 as documented by a physician or other health care provider in the progress note or chart.

Questions 148-150: Has the recipient experienced a grade 3 organ toxicity?



This question will enable only if the commercially available product 'Kymriah' is selected in question 1 and can only be completed on the 100 day and 6 month follow-up forms.

As defined by the CTCAE criteria, grade 3 toxicity represents severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living (ADL), which refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden. Other grade 3 toxicities / symptoms that are reported should be related to the cellular therapy infusion that are documented in the medical record as clinically important and relevant and do not fit into another category listed on this form.



Copy and complete questions 149-154 to report more than one grade 3 organ toxicity during this reporting period.

Specify the organ affected in question 149.

Specify the toxicity of that organ in question 150. The list of symptoms will dynamically filter based on the organ selected in question 149.

Organ / System	Symptom or Event
Cardiovascular	Capillary leak syndrome, cardiac arrhythmia, hypertension, hypotension, left ventricular systolic dysfunction, myocardial infarction, new or worsening heart failure, pericardial effusion, pericarditis, restrictive cardiomyopathy, thromboembolic event
Gastrointestinal	Abdominal pain, constipation, diarrhea, dyspepsia (heartburn), gastroenteritis, intestinal obstruction (includes small intestine and colonic), mucositis oral, nausea, vomiting
Kidneys	Acute kidney injury, chronic kidney disease, cystitis noninfective
Liver	Alanine aminotransferase increased (ALT), alkaline phosphatase increased, aspartate aminotransferase increased (AST), blood bilirubin increased, hepatic failure, hepatitis
Lungs	Acute respiratory distress syndrome, dyspnea, productive cough, pulmonary edema, respiratory edema, respiratory failure
Musculoskeletal	Arthralgia (joint pain), muscle weakness, generalized or specific area (not due to neuropathy), myalgia (muscle pain)
Nervous system	Dizziness, encephalopathy, headache, tremor
Other	Anorexia, chills, dysgeusia (taste alternation), edema limbs, fatigue

Questions 151: Was the date of onset previously reported?

If the grade 3 organ toxicity was diagnosed in a previous reporting period, symptoms continue into this

reporting period, and the date has already been reported, select **Yes** and continue with question 153. Else select **No** and report the date of grade 3 organ toxicity diagnosis in question 152.

Questions 152: Date of onset:

Report the date (YYYY-MM-DD) when the grade 3 organ toxicity was documented by either a physician/ health care provider or determined by lab results.

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

Questions 153-154: Did the grade 3 organ toxicity resolve?

If the grade 3 organ toxicity resolved, select “yes” in question 153 and report the date (YYYY-MM-DD) in question 154 as documented by a physician or other health care provider in the progress note or chart.

Questions 155-161: Has the recipient experienced a grade 4 organ toxicity?



This question can only be completed on the 100 day and 6 month follow-up forms.

As defined by the CTCAE criteria, grade 4 toxicity represents life-threatening consequences and urgent intervention is indicated. Other grade 4 toxicities / symptoms that are reported should be related to the cellular therapy infusion that are documented in the medical record as clinically important and relevant and do not fit into another category listed on this form.



Copy and complete questions 156-161 to report more than one grade 4 organ toxicity during this reporting period.

Specify the organ affected in question 156.

Specify the toxicity of that organ in question 157. The list of symptoms will dynamically filter based on the organ selected in question 156.

Organ / System	Symptom or Event
Cardiovascular	Capillary leak syndrome, cardiac arrhythmia, hypertension, hypotension, left ventricular systolic dysfunction, myocardial infarction, new or worsening heart failure, pericardial effusion, pericarditis, restrictive cardiomyopathy, thromboembolic event
Gastrointestinal	Abdominal pain, constipation, diarrhea, dyspepsia (heartburn), gastroenteritis, intestinal obstruction (includes small intestine and colonic), mucositis oral, nausea, vomiting
Kidneys	Acute kidney injury, chronic kidney disease, cystitis noninfective

Liver	Alanine aminotransferase increased (ALT), alkaline phosphatase increased, aspartate aminotransferase increased (AST), blood bilirubin increased, hepatic failure, hepatitis
Lungs	Acute respiratory distress syndrome, dyspnea, productive cough, pulmonary edema, respiratory edema, respiratory failure
Musculoskeletal	Arthralgia (joint pain), muscle weakness, generalized or specific area (not due to neuropathy), myalgia (muscle pain)
Nervous system	Dizziness, encephalopathy, headache, tremor
Other	Anorexia, chills, dysgeusia (taste alternation), edema limbs, fatigue

Questions 158: Was the date of onset previously reported?

If the grade 4 organ toxicity was diagnosed in a previous reporting period and symptoms continue into this reporting period and the date has already been reported, select **Yes** and continue with question 160. Else select **No** and report the date of grade 4 organ toxicity diagnosis in question 159.

Questions 159: Date of onset:

Report the date (YYYY-MM-DD) when the grade 4 organ toxicity was documented by either a physician / health care provider or determined by lab results.

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

Questions 160-161: Did the grade 4 organ toxicity resolve?

If the grade 4 organ toxicity resolved, select **Yes** in question 160 and report the date (YYYY-MM-DD) in question 161 as documented by a physician or other health care provider in the progress note or chart.

Questions 162-170: Specify the laboratory values collected (check all that apply)



Specify the maximum lab results since the date of last report. If there are multiple results available for the same test, only report the maximum in the reporting period.

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. Specify the maximum value since the date of the last report in question 163 and the date the sample was collected in question 164.

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. Specify the maximum value since the date of the last report in question 165 and the date the sample was collected in question 166.

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. Report the maximum value since the date of the last report in question 167 and the date the sample was collected in question 168.

Total serum ferritin: Ferritin is an acute phase reactant and is often found in high concentration in highly inflammatory conditions. Report the maximum value since the date of the last report in question 169 and the date the sample was collected in question 170.

None: None of the specified laboratory tests above were performed


Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
132	5/12/2021	Add	Added new example 4 for determining hypogammaglobulinemia resolution date	Provide clarity to reporting resolution date.
132	1/7/2021	Add	Added examples of when to report or not report hypogammaglobulinemia	Provide clarity of when to report hypogammaglobulinemia.
134	1/7/2020	Add	Added examples for hypogammaglobulinemia onset date	Provide clarity to reporting onset date.
135	1/7/2020	Add	Added examples for hypogammaglobulinemia resolution date	Provide clarity to reporting resolution date.
137	1/7/2020	Add	Clarified how to report continuation of IVIG therapy with this sentence: If the last immunoglobulin replacement therapy (IVIG) was given less than 3 months from the date of contact, report Yes unless it's clearly stated in the medical record that no more immunoglobulin replacement therapy is required.	Provide clarity of reporting IVIG continuation near the end of the reporting period.

Last modified: May 12, 2021

Q171-175: Infection

Infections occur frequently in recipients of cellular therapy or transplant. Questions 171-175 are intended to capture detailed information on clinically significant infections diagnosed during the reporting period. A single infection may be found on multiple cultures or at multiple sites. Infections may recur following resolution of symptoms and negative testing. Use the instructions provided in this section to determine when an infection should be considered clinically significant, and therefore reported, as well as when to report new and / or recurrent infections.

 **Diagnosis of COVID-19 after the start of the lymphodepleting therapy:** Any COVID-19 infections diagnosed after the start of the lymphodepleting therapy should be reported in questions 171 – 175 on the Cellular Therapy Essential Data Follow-Up (4100) form. An associated Respiratory Virus Post-Infusion Data (2149) form will be generated.

Question 171-175: Did the recipient develop a clinically significant infection since the date of the last report?

Indicate whether the recipient developed a clinically significant bacterial, viral, or fungal infection during the reporting period. For the purpose of this manual, the term “clinically significant” refers to any infection requiring treatment. Surveillance cultures in which normal flora is present and the recipient is asymptomatic do not need to be reported. If no clinically significant infections occurred during the reporting period, report “no” for question 171 and skip to question 176.

Do **not** report the following scenarios:

- Culture-negative neutropenic fever without clear source;
- Suspected (unconfirmed) viral or bacterial infections;
- Upper respiratory infections which are presumed viral, but no virus has been identified;
- Candida detected in oral or stool samples (includes oral thrush);
- Toenail fungus;
- Yeast infection in the groin, vagina, or under the breasts;
- Surveillance cultures in which normal flora is present and the recipient is asymptomatic;
- Infections persisting from a prior reporting period (including infections which have progressed to new sites since the last report); or
- Infections recurring within the time frames specified in the Definitions for Same Infection table below.

If an organism is identified by molecular report, laboratory report, or other physician documentation, the infection should be reported in questions 172-175. If no organism is identified, the center should use the following guidelines to determine whether to report an infection:

- If a fungal infection is suspected (per radiology assessments), but no organism is isolated during the reporting period, report the suspected infection in question 172 – 175.

- If a bacterial or viral infection is suspected, but not confirmed, do not report an infection in questions 172 – 175.
- If no particular organism group is identified or suspected, do not report an infection in question 172 – 175.

For each infection, report the organism, site, and date of diagnosis.

Definitions for Same Infection

Bacteria	Virus	Fungal
<p>≤ 7 Days</p> <ul style="list-style-type: none"> • Any bacteria 	<p>≤ 14 Days</p> <ul style="list-style-type: none"> • Adenovirus • Enterovirus • Herpes zoster • Influenza • Parainfluenza • Rhinovirus • Respiratory syncytial • Varicella zoster 	<p>≤ 14 Days</p> <ul style="list-style-type: none"> • Any yeasts
<p>≤ 30 Days</p> <ul style="list-style-type: none"> • Clostridium difficile 	<p>≤ 30 Days</p> <ul style="list-style-type: none"> • Human Herpes Virus - 6 	<p>≤ 90 Days</p> <ul style="list-style-type: none"> • Any molds
<p>≤ 365 Days</p> <ul style="list-style-type: none"> • Helicobacter pylori 	<p>≤ 60 Days</p> <ul style="list-style-type: none"> • Cytomegalovirus • Epstein-Barr virus • Herpes simplex • Polyomavirus 	

Organism:

Select the identified or suspected organism as reported on the microbiology report, laboratory report, or other physician documentation. If the specific organism is not listed, use the code **777 – Other organism** and report the name of the organism in the space provided. If a fungal infection is suspected, but not identified, report using code **503 – Suspected fungal infection**. As noted above, only report infections which are clinically significant.

Site:

Infections can occur virtually anywhere. In order to capture sufficient detail without excess burden, there is a list for the potential sites. An infection may occur in more than one site at the same time or at different times.

- If the infection is identified at multiple sites with the same organism and within the recurrence interval to be considered the same infection (Definitions for Same Infection table), please report all sites the organism was identified.
- If the infection is identified at multiple sites with an organism already reported but is outside of the

recurrence interval to be considered the same infection, please report as a new infection.

Select the site(s) of the infection from the options provided on the form. Report all sites of infection which were confirmed by microbiology, laboratory report, or other physician documentation during the reporting period. This includes any new sites identified after the date of diagnosis as well as after treatment has been initiated.

For clarification, the following site definitions are provided:

Blood: includes blood obtained from a central IV line, catheter tip, or from a direct needle stick (Peripheral draw). Blood should be the reported site for infections identified in the bone marrow.

Bone: an infection in the bone itself (Osteomyelitis)

CNS: includes CSF (cerebrospinal fluid) specimens as well as abscesses and/or inflammation noted on brain imaging (encephalitis, meningitis)

Eyes: includes infection in any part of the eye (i.e. retinitis)

Genital: includes vagina, penis, perineum, ovaries, scrotum, testes, uterus

GI tract, lower: includes jejunum, ileum, colon, rectum, and stool

GI tract, upper: includes mouth, dentition, esophagus, stomach, and duodenum

Joints: includes fibrous connective tissue and cartilage at any site of bone articulation, typically isolated to a single area (i.e., not a diffuse infection) such as the knee, elbow, or shoulder

Liver/Spleen: includes the gallbladder and biliary tract

Lung: also known as the lower respiratory tract

Skin, cellulitis: a spreading bacterial or viral infection of the skin and tissues beneath the skin

Skin, necrotizing fasciitis: a severe bacterial infection of the fascia, the tissues that line and separate muscles, that causes extensive tissue death including damage to skin and overlying tissues

Sinus and/or upper respiratory tract: all areas from the nose to the throat and sinuses, does not include lungs (report as "Lung"), mouth, or dental infections (report mouth and dental as "GI tract, upper").

Urinary tract, lower: includes urinary tract infections and cystitis (bladder inflammation)

Urinary tract, upper: includes the kidneys and ureters

Date of Diagnosis:

Report the date of diagnosis of the infection as the collection date for the positive microbiology culture or laboratory report. For suspected fungal infections, enter the date of a radiological test or the date treatment was started as the date of diagnosis. If multiple sites of infection are identified during the reporting period, report the collection date of the first positive microbiology culture or laboratory report.

Copy and complete questions 172-175 to report more than one infection during this reporting period.

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

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021

Q176-177: Pregnancy Status

Questions 176-177

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

If a pregnancy is reported, complete the Pregnancy (3501) Form to answer questions specific to the pregnancy. The option of **Previously reported** should only be used if the same pregnancy instance has already been reported on a Pregnancy (3501) Form that was created as an unscheduled form (“on demand”). If there is a question regarding use of this option, contact CIBMTR Center Support if there are questions.

Question 176: Was the recipient pregnant at any time in this reporting period? (Female Only)

Indicate Yes or No if the female recipient was pregnant at any time during the reporting period. If Yes, complete a Pregnancy (3501) form. See examples below.

Question 177: Was the recipient’s female partner pregnant at any time in this reporting period? (Male only)

Indicate **Yes** or **No** if the male recipient’s female partner was pregnant at any time during the reporting period. If *Ye*s, complete a Pregnancy (3501) form. See examples below.

Example 1. Recipient or recipient’s female partner becomes pregnant at day +68. It is reported at the time the 100-day Form Cellular Therapy Essential Data Follow-Up (4100) form is completed. Question 180 or 181 should be answered as ‘yes’, and the Form 3501 should be completed to report all pregnancy information.

Example 2. Recipient or recipient’s female partner becomes pregnant at day +68 and had received a commercially available CAR-T product (e.g. Yescarta®). Per protocol, the pregnancy should be reported at the time of knowledge of the pregnancy. The Form 3501 should be created as an unscheduled form in FormsNet3 and completed in a timely manner. When the 100-day Cellular Therapy Essential Data Follow-Up (4100) form is completed, question 180 or 181 should be answered as ‘previously reported’.

Example 3. Recipient or recipient’s female partner becomes pregnant at 1 year and 1 month and had received a commercially available CAR-T product (e.g. Yescarta®). Per protocol, the pregnancy should be reported at the time of knowledge of the pregnancy. The Form 3501 should be created as an unscheduled form in FormsNet3 and completed in a timely manner. The outcome of the first pregnancy does not go to term or does not result in a live birth and another pregnancy event occurs at 1 year and 11 months. It is decided to report the 2nd pregnancy event on the 2 year Cellular Therapy Essential Data Follow-Up (4100) form since it is due. Question 180 or 181 should be answered as ‘yes’ to create another Form 3501.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jan 22, 2021