2300: Greater Than 2 Years Post-HCT (Rev 3)

A transplant center designated as a *Comprehensive Report Form* center will submit data on the Pre-TED Form, followed by either the Post-TED Form or the Comprehensive Report Forms. The type of follow-up forms required for a specific recipient is determined by the CIBMTR's form selection algorithm (see General Instructions, Center Type and Data Collection Forms).

The Greater than Two Years Post-HCT Form (2300) must be completed annually through year 6, then biannually starting with year 8. The following recipient data should be collected from an actual examination, as close to the above time points as possible, by the transplant center physician or the local physician who is following the recipient post-HCT: vital status, functional status, acute graft-versus-host disease (GVHD), chronic GVHD, new malignancy, other organ impairment/disorder, subsequent HCT, and donor cellular infusion (DCI) information.

Subsequent HCT:

If this form reports a subsequent stem cell infusion, report data from the start of the first preparative regimen to the day before the preparative regimen begins for the subsequent HCT. If no preparative regimen is given for the subsequent transplant, report data from the start of the first preparative regimen to the day before the subsequent HCT. When reporting the date of actual contact (question 2), report the dates specified above (either the date the day before subsequent preparative regimen begins or date the day before subsequent transplant), regardless of whether there is actual patient contact on that date. This is an exception to standard date-of-contact reporting to ensure all dates are captured within the sequence of forms when reporting subsequent HCTs.

If a recipient receives a subsequent HCT the Comprehensive Research Form sequence will start over again with a Pre-TED Form (2400) and another Baseline Form (2000). **For recipients of multiple transplants, transplant centers are not granted access to the new Pre-TED Form in FormsNet3^{SM} until the Form 2100/2200/2300 from the previous transplant has been completed.** Transplant centers can use the FormsNet3^{SM} application to determine if a Pre-TED is due by either: 1) accessing the Forms Due Report, or 2) entering the recipient's unique ID (CRID) in the Patient Forms Due field. Contact your center's CIBMTR CRC if you have questions about the forms due for a recipient.

> ! If the recipient receives an **autologous HCT as a result of a poor graft or graft failure**, the Comprehensive Research Form sequence will **not** start over again. Generally this type of infusion (autologous rescue) is used to treat the recipient's poor graft response, rather than to treat the recipient's disease, and is therefore not considered a subsequent HCT.

Lost to Follow Up:

Occasionally, centers may lose contact with recipients for a variety of reasons, including their moving, changing physicians, or death. If contact with a recipient appears lost, please consider calling the recipient at home or work, sending a letter, communicating with the treating or referring physician, contacting the hospital billing department, or beginning a search request with the CIBMTR. If your center receives documented information that a recipient is alive or dead, the form should be filled out with the recipient vital status. If no documentation exists and several unsuccessful attempts have been made to contact the recipient, they are considered lost to follow-up, and the center should indicate this status in FormsNet for each reporting period in which no contact exists.

Q1-5: Vital Status
Q6-10: Functional Status
Q11-58: Acute Graft vs. Host Disease
Q59-130: Chronic Graft vs. Host Disease
Q131-173: New Malignancy
Q174-215: Other Organ Impairment / Disorder
Q216-223: Subsequent HCT
Q224-332: Donor Cellular Infusion (DCI) Information

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

If you need to reference the historical Manual Change History for this form, please click here or reference the retired manual section on the Retired Forms Manuals webpage.

Date	Manual Section	Add/ Remove/ Modify	Description
2/9/16	2300: Greater Than Two Years Post-HCT	Modify	Modified pediatric acute GVHD Gut guidelines to question 22. See table for details.
1/22/16	2300: Greater Than Two Years Post-HCT	Modify	Updated footnote 4 below acute GVHD staging and grading table: Persistent nausea with *or without* histologic evidence of GVHD in the stomach or duodenum.

6/26/15	2300: Greater Than Two Years Post-HCT	Modified	Added warnings to GVHD [Acute and Chronic] sections that state autologous and sygeneic HCTs should skip the applicable sections.
6/12/15	Manual-wide	Modify	Language relating to the Lost-to-Follow-Up (2802) has been removed.
6/12/15	2300: Greater Than Two Years Post-HCT	Add	Added text to question 22: Indicate the maximum grade of acute GVHD present during this reporting period [including acute GVHD that persists from a previous HCT or donor cellular infusion (DCI)]. If acute GVHD was present, but the maximum grade was not documented nor is it able to be determined from the grading and staging table, leave the maximum overall grade blank and override the error as "Unknown." **Example 1:** 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 Table 1. **Example 2:** A recipient developed acute liver GVHD with elevated LFTs 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 Table 1; "present, grade unknown" would be the best option to report.
6/5/15	2300: Greater Than Two Years Post-HCT	Add	Added pediatric acute GVHD Gut guidelines to question 22. See table for details.
6/5/15	2300: Greater Than Two Years Post-HCT	Add	Added text to questions 13 and 67: Do not report the results of a biopsy performed in an earlier reporting period; only report histologic confirmation during the reporting period in which the specimen was collected.
5/29/15	2300: Greater Than Two Years Post-HCT	Modify	Modified text in questions 262-268 to clarify FormsNet reporting: Report the total number of cells infused and specify the exponent for each cell type. If the cells were cryopreserved, report the totals after processing, but before cryopreservation. ~~If completing the paper version, copy this page to report more thanone infusion. -The FormsNet3SM application will allow as many infusion entries as needed for the 10-week period. (In Example 5, there would be 4 entries for the first 10-week period).~~ **If multiple cellular infusions were given within the 10-week period, report the cumulative total of all cells infused; submit a log of appended documents showing the product analyses for each individual DCI product.**

5/22/15	2300: Greater Than Two Years Post-HCT	Modify	Added “Oral Beclomethasone” to the following text in question 32-58: Note: An exception to this guidance would be the drugs budesonide **and oral beclomethasone**. They are drugs given by mouth for treatment of gut GVHD, but considered a “topical” since they’re not absorbed.

Q1-5: Vital Status

Question 1: Is the data reported on this form based on contact with the physician?

If the data reported on this form is based on contact with the physician, select “yes.” If the data is based on some other form of contact, select “no.”

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

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

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

Form	Time Point	Approximate Range
Greater Than Two Years Post-HCT (Form 2300)	Annually through Year 6 (i.e. Year 3, Year 4, etc.), then biannually starting with Year 8	+/- 30 days (Months 35-37, Months 47-49, 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 available.

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

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

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

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

What to report:
100 Day Date of Contact: 3/1/13 (Since there was no contact closer to the ideal date of 4/11/13, this date is acceptable)
6 Month Form: Indicate the recipient is lost to follow-up in FormsNet
1 Year Date of Contact: 1/4/13 (note the latest disease assessment would likely be reported as 1/1/13)

Additional Information

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

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

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

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

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

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

What to report:
100 Day Date of Contact: 4/23/13 (note the latest disease assessment would likely be reported as 4/22/13)
6 Month Date of Contact: 7/16/13 (note the latest disease assessment would likely be reported as 6/25/13)

Date of Contact & Subsequent Transplant

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

Example 5. The recipient had a 2nd transplant with a preparative regimen.
The recipient has their first transplant on 1/1/13 and a planned second transplant on 2/1/13. The recipient was admitted on and received their first dose of chemotherapy for the preparative regimen for HCT #2 on 1/28/13.

What to report:
100 Day Date of Contact: 1/27/13 (regardless of actual contact on that date)

Example 6. The recipient had a subsequent transplant without a preparative regimen.
Following their first transplant on 1/1/13, a recipient with SCID required a subsequent allogeneic transplant due to poor graft function. The recipient has remained inpatient following the first transplant. The physician planned the second transplant for 5/31/13, and proceeded without a preparative regimen.

What to report:
100 Day Date of Contact: 4/11/13 (+/- 15 days)
6 Month Date of Contact: 5/30/13

> **Reporting Date of Actual Contact for Subsequent HCTs**
> When reporting the date of actual contact prior to a subsequent HCT, report the dates specified above regardless of whether there is actual patient contact on the date. This is an exception to standard date of contact reporting to ensure all dates are captured within the sequence of forms.

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

Question 3: Did the recipient receive a subsequent HCT (bone marrow, mobilized peripheral blood stem cells, cord blood) since the date of contact from the last report?

Indicate whether the recipient received a second (or third, etc.) stem cell infusion. Stem cells are defined as mobilized peripheral blood stem cells, bone marrow, or cord blood. The source of the stem cells may be allogeneic unrelated, allogeneic related, or autologous. For more information on how to distinguish infusion types (example: HCT versus DCI), see Appendix O.

If "yes," the answers to the subsequent questions should reflect the clinical status of the recipient immediately prior to the start of the preparative regimen for subsequent HCT. If no preparative regimen is given, the answers to the subsequent questions should reflect the clinical status of the recipient immediately prior to the subsequent HCT. Also, complete Subsequent HCT section (questions 216-223). **Some data regarding the subsequent HCT (questions 216-223) are reported on this form even though these data fall outside of the reporting period for this form.**

> **Reporting Subsequent HCTs**
> It is important to note that the date of the actual contact for the Form 2300 being completed should be *before* the date of a subsequent HCT. Also, even if the subsequent transplant date *falls outside of the reporting period for this form*, the answer to "did the recipient receive a subsequent HCT" must be "yes." Answering "yes" to this question triggers a subsequent Pre-TED form (2400) to be made due in FormsNet.

Question 4: Specify the recipient's survival status at the date of last contact

Indicate the clinical status of the recipient on the date of actual contact for follow-up evaluation.
If the recipient is alive, answers to subsequent questions should reflect the recipient's clinical status since the date of the last contact.

If the recipient has died, answers to subsequent questions should reflect the recipient's clinical status between HCT and their death. You will also need to complete a Recipient Death Data Form (2900).

Question 5: Has the recipient received a donor cellular infusion (DCI)?

A DCI is a form of cellular therapy that uses cells from the original donor, and is commonly used to create a graft-versus-leukemia/tumor (GVL/GVT) effect. The recipient does not receive a preparative regimen prior to receiving the donor cells because the purpose of a DCI is to activate the immune system rather than repopulate the marrow. The recipient may, however, be given therapy prior to the infusion for the purpose of disease control. The types of cells used in a DCI include, but are not limited to: lymphocytes, unstimulated peripheral blood mononuclear cells, dendritic cells, and/or mesenchymal cells.

A DCI should be reported for a recipient who received cells from the original donor without a preparative regimen. However, **if the recipient received an additional infusion due to engraftment problems** (e.g., no engraftment, partial or poor engraftment, loss of graft, or late graft failure), **or if cells from a different donor are used, report this as a subsequent HCT, *not* a DCI.**

Indicate whether the recipient received a DCI during the reporting period. If “yes,” also complete the DCI information in questions 224-322.

For more information on how to distinguish infusion types (example: HCT versus DCI), see Appendix O.

Additional information regarding DCIs is available on the CIBMTR website: http://www.cibmtr.org/Meetings/Materials/CRPDMC/index.html

Q6-10: Functional Status

Question 6: Specify the functional status of the recipient on the date of last actual contact.

> ! If the recipient has died, skip this question and continue with question 7.

The CIBMTR uses the Karnofsky/Lansky scale to determine the functional status of the recipient on the date of contact.

The Karnofsky Scale is designed for recipients aged 16 years and older, and is not appropriate for children under the age of 16. The Lansky Scale is designed for recipients less than 16 years old.

Recipient performance status is a critical data field that has been determined to be essential for all outcome-based studies. Determination of performance status is ideally performed by a healthcare provider. Centers are encouraged to put tools in place to facilitate this collection. If a Karnofsky/Lansky score is not documented in the source documentation (e.g., inpatient progress note, physician's clinic note), data professionals are encouraged to discuss a determination with the healthcare provider rather than make an assignment themselves that may be based on inadequate information.

The CIBMTR recognizes that some transplant centers prefer to assign and use the ECOG performance score as opposed to the Karnofsky/Lansky score. Although the ECOG and Karnofsky/Lansky performance score systems are based on similar principles, the scales are not the same. For example, the Karnofsky/Lansky scale is described in 10 categories, whereas the ECOG performance status is reported in six categories. Due to the overlap between the two systems, an ECOG score of "one" can represent either "80" or "90" on the Karnofsky/Lansky scale; whereas, a Karnofsky/Lansky score of "80" or "90" is converted directly to an ECOG score of "one." Therefore, the Karnofsky/Lansky scale can be more accurately converted into ECOG.

However, for centers that collect only an ECOG performance score, CIBMTR will make the following accommodations when auditing the source data:

- Centers assigning ECOG scores should do so using standard practices to ensure accuracy.
- For the purposes of CIBMTR reporting, conversion of ECOG to Karnofsky/Lansky should follow a standard and consistent practice to account for the lack of direct mapping. This practice should be clear and reproducible.

Select the appropriate performance scale, Karnofsky or Lansky, based on the recipient's age. Using this scale, select the score (10-100) that best represents the recipient's activity status immediately prior to the date of last actual contact. Acceptable performance scores include those recorded within 14 days prior to 100-Day and Six-Month contact dates. For the annual reporting periods, performance scores may be reported if dictated within one month of the contact date. The only valid scores are 10-100; zero is not a valid response for this scale, nor are values not ending in zero, such as "85." The Karnofsky/Lansky scale can be found in Appendix L.

Questions 7-8: Specify the category which best describes the recipient's current occupation.

Select the category that best describes the recipient's current occupation. If the recipient is a student, check "student." If the recipient is younger than school-aged, check "under school age" and continue with question 11. If "other" is selected, report the recipient's occupation in question 8.

If the recipient is not currently employed or has died, check the box that best describes his/her last job.

Questions 9-10: What is the recipient's current or most recent work status during this reporting period?

Select the work status that best describes the recipient's current or most recent employment during this reporting period. If the recipient is retired, specify their retirement status in question 10.

Q11-58: Acute Graft vs. Host Disease (GVHD)

> **Autologous and Syngeneic Transplants**
> If this was an autologous or syngeneic HCT, continue with the New Malignancy section at question 131. The next two sections relate to graft-versus-host disease for allogeneic HCTs only.

Question 11: Did acute GVHD develop or persist (or a flare-up that was more severe) since the date of the last report?

Indicate whether acute GVHD developed, persisted, or flared-up (became more severe) during the reporting period in response to transplant or donor cellular infusion.

If “yes,” continue with question 12. If “no” or “unknown,” continue with question 59.

Question 12: 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 documenting it as acute GVHD versus a drug reaction). If the clinical diagnosis date is not documented, then report the date of histological confirmation.

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 recipient had a previous onset of GVHD that subsequently resolved for at least 30 days and then reactivated (“flare”), report the flare as a new episode and report the new date of diagnosis.

If the date of diagnosis is greater than 100 days post-HCT, verify the symptoms are related to acute GVHD versus chronic GVHD.

If the date was reported in a prior reporting period and acute GVHD has persisted, check “date previously reported.”

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

Question 13: Was the diagnosis based on evidence from a biopsy (histology)?

Histological tests may be performed to confirm the clinical diagnosis of GVHD; however, the staging and grading of GVHD should be based on clinical evidence, not histological results.

Indicate whether a biopsy was used to diagnose acute GVHD. If “yes,” continue with question 14. If “no,” continue with question 21. Do not report the results of a biopsy performed in an earlier reporting period; only report histologic confirmation during the reporting period in which the specimen was collected.

Questions 14-19: Specify result(s)

For each organ listed, indicate the test result documented on the laboratory report as either “positive,” “negative,” or “inconclusive.” If a biopsy was not completed, select “not tested.” If “other site” is selected, specify the site biopsied in question 19.

Question 20: Is a copy of the pathology report attached?

Attaching a copy of the diagnostic pathology report for acute GVHD reduces the need for later data queries.

If “yes,” complete the Log of Appended Documents (Form 2800) and attach the pathology report. For more information regarding the Form 2800, see the Log of Appended Documents manual section.

Question 21: Was the diagnosis based on clinical evidence?

Acute GVHD may damage the skin, gut, liver, or other organs. Clinical evidence of acute GVHD may include maculopapular rash, nausea, vomiting, diarrhea, and/or jaundice (elevated total bilirubin). Indicate whether clinical evidence was used to diagnose acute GVHD.

Question 22: Maximum overall grade of acute GVHD

The acute GVHD grading scale is based on clinical evidence (physician observation), not histology. If there is a difference in the clinical grade recorded by the physician and a histological report, use the data from the clinical documentation. 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 Table 1 below.

Table 1. GVHD Grading and Staging

Extent of Organ Involvement			
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] *Pediatric*: 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 *Pediatric*: 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 *Pediatric*: >833 ml/m^2/day or > 30 mL/kg/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dl	Severe abdominal pain with or without ileus
Grade[5]			
I	Stage 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	—	Stage 2-3 or	Stages 2-4
IV[6]	Stage 4	Stage 4	—

[1] Use “Rule of Nines” (Table 5) or burn chart to determine extent of rash.

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

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

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

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

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

Indicate the maximum grade of acute GVHD present during this reporting period [including acute GVHD that persists from a previous HCT or donor cellular infusion (DCI)].

If acute GVHD was present, but the maximum grade was not documented nor is it able to be determined from the grading and staging table, leave the maximum overall grade blank and override the error as “Unknown.”

Example 1: 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 Table 1.

Example 2: A recipient developed acute liver GVHD with elevated LFTs 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 Table 1; "present, grade unknown" would be the best option to report.

Question 23: Is acute GVHD still present at the date of contact for this report (question 2)?

Indicate whether the recipient has active clinical signs/symptoms of acute GVHD at the date of contact. Select "yes," "no," "progressed to chronic GVHD," or "unknown."

Questions 24-31: List the maximum severity of organ involvement

Skin: Select the stage that reflects the body surface area involved with a maculopapular rash. See Table 4 below to determine the percent of body surface area involved with a rash. If the recipient has acute GVHD but does not have skin rash, report "stage 0 – no rash." If the recipient has a skin rash that is not attributed to acute GVHD (e.g., due to a drug reaction or infection), report "no skin acute GVHD / rash not attributable to acute GVHD."

Table 5: 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%

Pediatric Recipients

Diarrhea in pediatric recipients is assessed in mL/m^2 rather than mL/kg since the recipient's weight may fluctuate due to cardiac failure, renal failure, or severe diarrhea.

Lower intestinal tract: Select the stage that reflects the volume of diarrhea. Use mL/day for adult recipients and mL/m^2/day for pediatric recipients. Input and output records may be useful in determining the volume of diarrhea. If the recipient has acute GVHD but does not have diarrhea, report "stage 0 – no diarrhea." If the recipient has diarrhea, but it is not attributed to acute GVHD (e.g., due to a drug reaction or infection), report "no gut acute GVHD / diarrhea not attributable to acute GVHD."

Upper intestinal tract: Select the stage that reflects the presence of persistent nausea or vomiting.

Liver: Select the stage that reflects the bilirubin level. If a recipient has evidence of acute GVHD but has a bilirubin level less than 2.0 mg/dL, select "stage 0 – bilirubin < 2.0 mg/dL." If the recipient has hyperbilirubinemia, but it is not attributed to acute GVHD (i.e., due to liver dysfunction not related to acute GVHD), select "no liver acute GVHD / bilirubin level not attributable to acute GVHD."

For recipients who have a normal bilirubin level with elevated transaminase levels and a liver biopsy documenting GVHD, report this in "Other clinical organ involvement."

Other clinical organ involvement: Indicate whether acute GVHD affected another organ. If "yes," continue with question 29. If "no," continue with question 32. If "other site" is selected (question 30), specify the site in question 31.

Questions 32-58: Was specific therapy used to treat acute GVHD since the date of the last report?

Indicate whether therapy was used to treat acute GVHD. If "yes," continue with question 33. If "no," continue with question 59.

For each agent listed, indicate whether or not it was used to treat acute GVHD. If "yes," answer any additional applicable questions.

Report prophylactic drugs if they were continued after the onset of acute GVHD.

ALS (anti-lymphocyte serum), ALG (anti-lymphocyte globulin), ATS (anti-thymocyte serum), ATG (anti-thymocyte globulin): 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.

Corticosteroids: Examples: dexamethasone, hydrocortisone, methylprednisolone, prednisone/prednisolone. "Systemic" refers to drugs given by mouth, intramuscularly (IM), or intravenously (IV). Report systemic corticosteroids on question 36. "Topical" refers to drugs applied to the skin, given as eye drops, or administered through inhalation therapy. Note: An exception to this guidance would be the drugs

budesonide and oral beclomethasone. They are drugs given by mouth for treatment of gut GVHD, but considered a “topical” since they’re not absorbed. but is considered a “topical” drug since it is not absorbed. Report topical corticosteroids on question 37.

Cyclosporine (CSA): Examples: Sandimmune®, Neoral®. Cyclosporine is usually given for ≥3 months.

ECP (extra-corporeal photopheresis): The recipient’s blood is exposed to ultraviolet light outside of their body and re-infused.

FK 506: Alternate names: tacrolimus, Prograf®. FK 506 inhibits the production of interleukin-2 by T-cells.

In vivo anti T-lymphocyte monoclonal antibody: Antibody preparations that are infused in the recipient following HCT. Specify the antibody used as: anti CD25 (Zenapax, Daclizumab, Anti-Tac), Campath®, entanercept (Enbrel®), and/or infliximab (Remicade®).

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

Methotrexate (MTX): Example: amethopterin. MTX inhibits the metabolism of folic acid.

Mycophenolate mofetil (MMF): Alternate name: CellCept®. MMF inhibits the de novo pathway used for lymphocyte proliferation and activation.

Sirolimus: Alternate names: rapamycin, Rapamune®. Sirolimus inhibits the response to interleukin-2, blocking the activation of T-cells.

Ursodiol: Suppresses synthesis and secretion of cholesterol from the liver and absorption in the intestines.

Blinded randomized trial: If the recipient is on a blinded randomized trial, specify the agent being studied in the trial. Additionally, update the Greater Than Two Year Post-HCT Forms (2300) once the trial is over to specify whether the recipient received the trial drug or placebo.

Other agent: Specify the other agent being given as GVHD treatment.

Alternate methods of treatment (example: psoralen and ultraviolet-A therapy [PUVA]) may be used in combination with drug therapy. If alternate methods were used, report in “other agent” (questions 57-58).

Q59-130: Chronic Graft vs. Host Disease (GVHD)

Autologous and Syngeneic Transplants
If this was an autologous or syngeneic HCT, continue with the New Malignancy section at question 131.

Question 59: Did chronic GVHD develop or persist (or a flare-up that was more severe) since the date of the last report?

Chronic GVHD affects 25-50% of long-term survivors of allogeneic transplants and usually develops after day 100. However, it has been documented as occurring as early as day 60 and as late as day 400 post HCT. In chronic GVHD, the mechanism of tissue damage differs from acute GVHD and a greater variety of organs may be affected.

Indicate whether chronic GVHD developed, persisted, or flared-up during the reporting period. A flare-up is the recurrence of chronic GVHD in the first 30 days following tapering/stopping of GVHD treatment. If “yes,” continue with question 60. If “no” or “unknown,” continue with question 129. If “no symptoms, but receiving treatment,” continue with question 97.

Question 60: Date of chronic GVHD diagnosis

Report the date of clinical diagnosis of chronic GVHD. The clinical diagnosis date may not necessarily be the date the symptoms began (example: the recipient developed dry eyes one week prior to the physician’s documenting the dry eyes as a manifestation of chronic GVHD). If the clinical diagnosis date is not documented, then report the date of histological confirmation.

If chronic GVHD progressed directly from acute GVHD, the date of onset should be reported as the date the recipient’s symptoms progressed from acute to chronic.

If chronic GVHD resolved and symptoms flared-up within 30 days of tapering or discontinuing treatment, report the initial date of GVHD diagnosis. If chronic GVHD flared up more than 30 days after treatment was tapered or discontinued, report the date the new episode of GVHD was diagnosed.

If the date was reported in a prior reporting period and chronic GVHD persisted, check “date previously reported” and continue with question, check “date previously reported” and continue with question 65.

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

Question 61: Onset of chronic GVHD was

Indicate whether the onset of chronic GVHD was:

- Progressive – acute GVHD progressed directly to chronic GVHD
- Interrupted – acute GVHD resolved for greater than 7 days, then chronic GVHD developed
- de novo – acute GVHD never developed
- chronic GVHD flare – symptoms reactivated within 30 days of tapering or discontinuing drug

Question 62: Karnofsky/Lansky score at diagnosis of chronic GVHD

The Karnofsky Scale is designed for recipients aged 16 years and older, and is not appropriate for children under the age of 16. The Lansky Scale is designed for recipients less than 16 years old.

Recipient performance status is a critical data field that has been determined to be essential for all outcome-based studies. Determination of performance status is ideally performed by a healthcare provider. Centers are encouraged to put tools in place to facilitate this collection. If a Karnofsky/Lansky score is not documented in the source documentation (e.g., inpatient progress note, physician's clinic note), data professionals are encouraged to discuss a determination with the healthcare provider rather than make an assignment themselves that may be based on inadequate information. The score determined by this discussion must be documented in the recipient record. Although the ECOG and Karnofsky/Lansky performance score systems are based on similar principles, the scales are not the same. For example, the Karnofsky/Lansky scale is described in 10 categories, whereas the ECOG performance status is reported in six categories. Due to the overlap between the two systems, an ECOG score of "one" can represent either "80" or "90" on the Karnofsky/Lansky scale; whereas, a Karnofsky/Lansky score of "80" or "90" is converted directly to an ECOG score of "one." Therefore, the Karnofsky/Lansky scale can be more accurately converted into ECOG.

However, for centers that collect only an ECOG performance score, CIBMTR will make the following accommodations when auditing the source data:

- Centers assigning ECOG scores should do so using standard practices to ensure accuracy.
- For the purposes of CIBMTR reporting, conversion of ECOG to Karnofsky/Lansky should follow a standard and consistent practice to account for the lack of direct mapping. This practice should be clear and reproducible.

Select the appropriate performance scale, Karnofsky or Lansky, based on the recipient's age. Using this scale, indicate the score (10-100) that best represents the recipient's activity status at diagnosis of chronic GVHD. The only valid scores are 10-100; zero is not a valid response for this scale, nor are values not ending in zero, such as "85." The Karnofsky/Lansky scale can be found in Appendix L.

Question 63: Platelet count at diagnosis of chronic GVHD

Report the lowest platelet count recorded within 14 days +/- of the diagnosis of chronic GVHD whether or not the recipient has received a platelet transfusion. Indicate the units.

Question 64: Diagnosis was based on

Select the method used to diagnose chronic GVHD.

Question 65: Maximum grade of chronic GVHD

The grading system for chronic GVHD is divided into two categories: limited and extensive.

Reporting Grade of Chronic GVHD (Sullivan KM, *Blood* 1981; 57:267.)
Limited: Localized skin involvement resembling localized scleroderma with or without liver involvement; no other organ involvement.
Extensive: Generalized skin and/or multiple organ involvement.

Indicate the maximum grade of chronic GVHD present during this reporting period.

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
- Involvement of the salivary glands or oral mucous membranes
- Involvement of any other target organ

Question 66: Overall severity of chronic GVHD

Currently there are no specific criteria for the severity of chronic GVHD. This subjective assessment should be reported as documented by the physician using the guidelines below.

- Mild: signs and symptoms of chronic GVHD do not interfere substantially with function and do not progress once appropriately treated with local therapy or standard systemic therapy (corticosteroids and/or cyclosporine or FK 506)
- Moderate: signs and symptoms of chronic GVHD interfere somewhat with function despite appropriate therapy or are progressive through first line systemic therapy (corticosteroids and/or cyclosporine or FK 506)
- Severe: signs and symptoms of chronic GVHD limit function substantially despite appropriate therapy or are progressive through second line therapy

Questions 67-96: Indicate if there was organ involvement with chronic GVHD

Indicate whether chronic GVHD affected each organ/system listed. If "yes," also indicate if the involvement was proven by histological evidence (biopsy). Do not report the results of a biopsy performed in an earlier reporting period; only report histologic confirmation during the reporting period in which the specimen was collected.

Skin: Ranges from skin discoloration to severe scarring and tightness. Includes, but is not limited to:

- Sclerosis: thickening of the skin, which may cause loss of suppleness
- Rash
- Ulcers
- Pruritis: itching of the skin
- Dyspigmentation: change in color of the skin. Usually erythema (redness) or vitiligo (loss of skin color)
- Alopecia: scalp hair loss
- Lichenoid skin changes: whitish lacy patches

Eyes: Recipients often have dry eyes and corneal ulcers due to keratoconjunctivitis sicca.

- Xerophthalmia: dry eyes
- Schirmer's test: a measure of tear production, decreased wetting <5 mm.
- Slit lamp: The binocular slit lamp examination provides stereoscopic magnified view of the eye structures in detail.
- Corneal erosion/conjunctivitis: ulcers on the cornea, usually quite painful, or inflammation of thin membrane covering the eye and inner lids.

Mouth: Refers to white plaques, scarring and ulcers occurring in the mouth and throat.

- Lichenoid changes: whitish lacy patches, usually appear first on inner cheeks, but can involve roof of mouth, gums, and/or tongue
- Mucositis/ulcers: similar to cold sores but they can involve any part of the mouth, important not to confuse with herpes simples infections
- Erythema: redness

Lung: This ranges from mild impairment on pulmonary function tests to severe disorders.

- Bronchiolitis obliterans (BO): literally, scarring of the small airways. Usually diagnosed by lung biopsy or pulmonary function tests (showing obstruction of airflow) Symptoms include shortness of breath (dyspnea), dry cough, and wheezing. **If bronchiolitis obliterans was a manifestation of chronic GVHD, also complete the Other Organ Impairment section, questions 174-215.**
- Other pulmonary involvement: include related pulmonary disorders here. Do not report interstitial pneumonitis (IPn). Report IPn in the Other Organ Impairment / Disorder section, questions 174-215.

Gastrointestinal tract (GI):

- Esophageal: may have difficulty swallowing (dysphagia), pain when swallowing (odynophagia), narrowing of esophagus (esophageal web), and/or poor motility (food does not move down esophagus normally).
- Chronic nausea/vomiting: either nausea or vomiting that occurs on at least 25% of days (1 out of 4 weeks) or occurs frequently enough to interfere with functioning and lifestyle.
- Chronic diarrhea: occurs on at least 25% of days (1 out of 4 weeks) or occurs frequently enough to interfere with functioning and lifestyle. This may occur due to thickening of the intestinal wall.
- Malabsorption: inability to digest or absorb the nutrients from food. Diagnosed with specific tests measuring fecal fat, xylose uptake, or vitamin levels.
- Abdominal pain or cramping.

Liver: Record all types of liver abnormalities, either clinical or histological.

- Liver involvement may be manifested by elevation of any of the liver function tests (bilirubin, particularly the direct component, alkaline phosphatase, GGT, SGOT [AST], and/or SGPT [ALT]).
- A liver biopsy may show obliteration of bile ducts (canaliculi) or cirrhosis.

Genitourinary tract (GU):

- Vaginitis/stricture: Pain, ulceration, inflammation, and/or eventual scarring/narrowing of the vaginal opening.

Musculoskeletal: refers to pain, contractures, and/or joint deformities.

- Arthritis: inflammation of joints
- Contractures: loss of joint mobility due to skin changes
- Myositis: inflammation of muscles
- Myasthenia: weakness of muscles

Hematologic: involving the blood system

- Thrombocytopenia: decreased platelet count (<100,000).
- Eosinophilia: elevation in percent eosinophils in blood (>5% of upper limit normal for your institution).
- Autoantibodies: any abnormal antibody against the patient's normal bodily tissue (for example, antinuclear antibody [ANA], red cell autoantibodies [if directed against patient's own blood type]).
- Other hematologic involvement: not classifiable above, specify the involvement.

Other:

- Serositis: inflammation of a serous membrane, specify the site.
- Weight loss.
- Other organ involvement from chronic GVHD: specify the additional site in question 96.

Questions 97-127: Was specific therapy used to treat chronic GVHD?

Indicate whether therapy was used to treat chronic GVHD. If "yes," continue with question 98. If "no," continue with question 128.

For each agent listed, indicate whether or not it was used to treat chronic GVHD. If "yes," answer any additional questions if applicable.

Report prophylactic drugs if they were continued after the onset of chronic GVHD.

Refer to questions 32-58 for a description of most agents listed. "Systemic" refers to drugs given by mouth, intramuscularly (IM), or intravenously (IV). "Topical" refers to drugs applied to the skin, given in eye drops,

or administered through inhalation therapy. Note: the drug budesonide is an exception. It is a drug given by mouth for treatment of gut GVHD, but it is considered a “topical” drug since it is not absorbed.

Additional Agents:

Azathioprine: Example: Imuran®. Azathioprine inhibits purine synthesis. Usually it is used at low doses in combination with other treatments.
Etretinate: A synthetic derivative of vitamin A.
Hydroxychloroquine: Example: Plaquenil®. Hydroxychloroquine inhibits transcription of DNA to RNA and is commonly used as an anti-malarial drug.
Lamprene®: Example: Lamprène®, Clofazimine. Lamprene acts as an anti-inflammatory agent.
Pentostatin: Inhibits adenosine deaminase which blocks DNA, and some RNA, synthesis.
PUVA (Psoralen and UVA): Psoralen is applied or taken orally to sensitize the skin, and then the skin is exposed to UVA.
Thalidomide: Was once used as an anti-nausea medication in pregnant women, but was found to cause severe birth defects. Currently, thalidomide is used for its anti-inflammatory properties as well as in combination with dexamethasone for the treatment of Multiple Myeloma.

Alternate treatments may be used in combination with drug therapy (example: low dose cyclophosphamide). If alternate treatments were used, report in “other agent” (questions 126-127).

Question 128: Are symptoms of chronic GVHD still present on the date of actual contact (or present at the time of death)?

Indicate whether the recipient has active clinical signs/symptoms of chronic GVHD still present on the date of contact (question 2). If the recipient has died, indicate whether chronic GVHD symptoms were present at the time of death.

Only report “no” if the recipient has no symptoms.

Question 129: Is the recipient still taking immunosuppressive agents (including PUVA) to treat or prevent GVHD?

Indicate whether the recipient is still taking immunosuppressive agents to treat or prevent GVHD on the date of contact. If “no,” continue with question 130. If “yes” or “unknown,” continue with question 131.

Do not include local or topical therapies.

This question must be answered for all allogeneic transplants, whether or not the recipient developed GHVD.

If the recipient has died prior to the discontinuation of immunosuppressive agents used to treat or prevent GHVD, select “yes.”

Question 130: Date final treatment administered

Report the date the final treatment or prophylaxis dose was administered.

If the month and year that the immunosuppressive agents were discontinued is known, enter this information. Do not select “unknown” in this situation.

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

Q131-173: New Malignancy

Question 131: Did a new malignancy, lymphoproliferative or myeloproliferative disorder develop since the date of the last report that is different from the disease for which the HCT was performed?

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

Report relapse of the recipient's primary disease on the appropriate post-HCT Disease Data Form. Relapse of a prior malignancy will not be captured by the CIMBTR.

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

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

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

- Recurrence of primary disease (report as relapse or disease progression)
- Relapse of malignancy from recipient's pre-HCT medical history
- Breast cancer found in other (i.e., opposite) breast (report as relapse)
- Post-HCT cytogenetic abnormalities associated with the pre-HCT diagnosis (report as relapse)
- Transformation of MDS to AML post-HCT (report as disease progression)

Skin Cancers
For most malignancies, one does not report recurrence, progression or transformation of the recipient's primary disease (disease for which the transplant was performed) or relapse of a prior malignancy in the "New Malignancy" section. However, in the case of a basal cell or squamous cell skin cancer, one needs to report each discrete episode. For example, a recipient had a basal cell skin cancer diagnosed on the neck four months post-HCT and six months later had another basal cell located on the nose. The lesion on the nose is not

considered a metastasis from the neck, but a new discrete lesion. These discrete episodes should be reported in the "Other skin malignancy" questions on the Greater Than Two Year forms (revision 3, question 159-161).

If a new malignancy, lymphoproliferative disorder, or myeloproliferative disorder has occurred following the HCT, check "yes" and continue with question 132. If not, check "no" and continue with question 174.

Question 132: For all new malignancies except for "other skin malignancy (basal cell, squamous)," was testing performed to determine the cell of origin?

Indicate whether testing was performed on the malignant tumor cells to determine the cell origin of the new malignancy. If "yes," continue with question 133. If "no," continue with question 135.

Select "the only new malignancy in this reporting period was 'other skin malignancy (basal cell, squamous)'" if other skin malignancy (basal cell, squamous) was the only new malignancy identified.

Question 133: Specify the cell of origin of the new malignancy

Indicate whether the new malignancy originated in cells from the recipient (host), donor, or an unknown origin.

Question 134: Is a copy of the cell origin evaluation (VNTR, cytogenetics, FISH) attached?

Attaching a copy of the evaluation for the cell origin assists in disease confirmation and **reduces the need for later data queries.**

If "yes," complete the Log of Appended Documents (Form 2800) and attach the pathology report. For more information regarding the Form 2800, see the Log of Appended Documents manual section.

Questions 135-172: Specify which new disease(s) occurred and if applicable, the date of diagnosis.

For each malignancy, lymphoproliferative disorder, or myeloproliferative disorder listed, check "yes" or "no." If "yes," enter the date of diagnosis of the corresponding malignancy, lymphoproliferative disorder, or myeloproliferative disorder and answer any additional questions if applicable.

The "other malignancy, specify" category should be used to report any subcategories of new malignancies that are not listed on the form.

Question 173: Is a pathology / autopsy report or other documentation attached?

Attaching a copy of the diagnostic pathology or autopsy report for the new malignancy assists in disease confirmation and **reduces the need for later data queries.** Include information regarding the histological diagnosis, site(s) of disease, and any applicable ancillary information available.

If “yes,” complete the Log of Appended Documents (Form 2800) and attach the pathology report. For more information regarding the Form 2800, see the Log of Appended Documents manual section.

Q174-215: Other Organ Impairment / Disorder

Question 174: Has the recipient developed any other clinically significant organ impairment or disorder since the date of the last report?

The intent of this question is to identify *serious* conditions that have an effect on the outcome of the HCT. For the purposes of this manual, the term "clinically significant" refers to conditions that are being treated post-HCT, or have caused complications post-HCT. Do not report complications that are expected for most transplant recipients (example: mild-to-moderate mucositis).

Indicate whether the recipient developed any other clinically significant organ impairment or disorder since the date of the last report. If "yes," continue with question 175. If "no," continue with question 216.

Questions 175-215: Specify impairment/disorder and the date of diagnosis

For each organ impairment and/or disorder listed, check "yes" or "no." If "yes," enter the date of diagnosis of the corresponding impairment/disorder.

Avascular necrosis: localized tissue death due to inadequate oxygen to the cells. Also known as coagulation necrosis or ischemic necrosis.
Bronchiolitis obliterans (BO): BO is an obstructive complication which affects the small airways.
Cataracts: loss of transparency in the lens of the eye.
Congestive heart failure (CHF): inability of the heart to supply oxygenated blood to meet the body's needs. Ejection fraction < 40%.
Cryptogenic organizing pneumonia (COP): COP, also known as idiopathic bronchiolitis obliterans with organizing pneumonia (BOOP), is a restrictive pulmonary complication which affects the alveoli and alveoli ducts.
Diabetes/hyperglycemia: high blood glucose levels. Diabetes/hyperglycemia should only be reported if insulin and/or oral medication is required for treatment. Diabetes/hyperglycemia controlled through diet and exercise should not be reported.
Gonadal dysfunction/infertility requiring hormone replacement: Females may experience early symptoms of menopause including amenorrhea. Males may experience decreased spermatogenesis. Low levels of follicle stimulating hormone (FSH), luteinizing hormone (LH), and/or testosterone may require hormone replacement therapy.
Growth hormone deficiency: a condition in which the body does not produce enough growth hormone.
Growth disturbance: a reduced overall rate of growth.
Hemorrhagic cystitis/hematuria requiring medical intervention: characterized by bleeding and inflammation of the bladder wall. Hemorrhagic cystitis may result from systemic or radiation therapy and/

or some viral infections. Report cases with macroscopic (visible to the naked eye) or gross hematuria (WHO Grade III and IV hemorrhagic cystitis). Examples of medical intervention include: catheterization of bladder, extra transfusions, or a urology consult.

Hypothyroidism: decreased activity of the thyroid gland. Diagnosis of hypothyroidism includes high levels of thyroid-stimulating hormone (TSH). Symptoms of hypothyroidism include fatigue, depression, weakness, weight gain, musculoskeletal pain, decreased taste, hoarseness, and/or puffy face.

Interstitial Pneumonitis (IPn)/ARDS: Interstitial pneumonitis or ARDS can result from infectious or non-infectious causes. Infectious causes may be bacterial, viral (CMV, adenovirus, RSV, influenza, etc.), or fungal. Interstitial pneumonitis may also be idiopathic (no organism was isolated).

Myocardial infarction (MI): an obstruction in the coronary artery resulting in damage/necrosis to the cardiac muscle.

Non-Infectious Liver Toxicity: cirrhosis, hepatic veno-occlusive disease (VOD; not GVHD related), or other non-infectious liver abnormalities.

Pancreatitis: inflammation of the pancreas.

Post-transplant microangiopathy thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), or similar syndrome:

Features include:

- microangiopathic hemolysis
- thrombocytopenia (< 50 × 10^9/L)
- LDH greater than the center-specific upper limit of normal
- serum creatinine > 2 mg/dL or > 50% rise over baseline
- neurological changes
- bilirubin greater than twice the center-specific upper limit of normal
- pulmonary involvement

Pulmonary Hemorrhage: bleeding lung tissue, including diffuse alveolar hemorrhage (DAH).

Renal failure severe enough to warrant dialysis: report whether dialysis was ordered or recommended for renal failure. Also report whether the recipient received the treatment. Symptoms of renal failure include dehydration, nausea, blood in the urine, and/or swelling of extremities.

Stroke: loss of brain function due to a disturbance in the blood supply to the brain.

Seizure: sudden, involuntary muscle contractions due to the hyperexcitation of neurons.

For each organ impairment and/or disorder listed, check “yes” or “no.” If “yes,” enter the date of diagnosis of the corresponding impairment/disorder. If the diagnosis was determined at an outside center and no documentation of a clinical, pathological, or laboratory assessment is available, the dictated date of diagnosis within a physician note may be reported.

The “other impairment or disorder, specify” category should be used to report any clinically significant impairment(s)/disorder(s) not listed on the form. Examples may include but are not limited to:

- Non-infectious eye complications (retinopathy due to radiation therapy)
- Bone abnormalities (aseptic necrosis, osteoporosis)
- Grade 4 mucositis (including anywhere along the digestive tract), reporting the first instance of grade 4 disease (e.g., the date of initiation of total parenteral nutrition (TPN))

Do not report complications that have been reported elsewhere on the form.

Q216-223: Subsequent HCT

Complete this section if the recipient received a subsequent HCT (question 3, answered "yes"). If no subsequent HCTs were performed, continue with the DCI section at question 224.

In addition to this section, a new Pre-TED Form (2400) and Recipient Baseline Data Form (Form 2000) must be completed for the subsequent HCT. The exception to this is an *autologous HCT performed for engraftment reasons* (indications 1-3 in question 219). The cells used for this subsequent autologous HCT would have been collected prior to the previous transplant.

For information on how to distinguish infusion types (e.g., HCT versus DCI), see Appendix O.

Question 216: Date of subsequent HCT

Report the date of the subsequent HCT.

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

Question 217: Was the subsequent HCT performed at a different institution?

Indicate if the subsequent HCT was performed at another institution. If "yes" continue with question 218. If "no," continue with question 219.

Question 218: Specify the institution that performed the subsequent HCT

Report the name, city, state and country of the institution where the recipient's subsequent HCT was performed. These data are used to identify and link the recipient's existence in the database.

Questions 219-220: What was the indication for subsequent HCT?

Indicate the reason for the subsequent HCT (check only one).

- **No hematopoietic recovery.** Additional stem cells are required because neutrophil recovery was not achieved following previous high-dose therapy and HCT (i.e., ANC was never ≥ 0.5×10^9/L for three consecutive days). A subsequent autologous HCT for no hematopoietic recovery does not require an additional Pre-TED (Form 2400) or Baseline (2000) to be completed.
- **Partial hematopoietic recovery.** Additional stem cells are required because hematopoietic recovery was deemed insufficient or too slow for survival following previous high-dose therapy and HCT. A

subsequent autologous HCT for partial hematopoietic recovery does not require an additional Pre-TED (Form 2400) or Baseline (2000) to be completed.

- **Graft failure/rejection after achieving initial hematopoietic recovery.** Additional stem cells are required because the hematopoietic recovery indefinitely declined after the initial hematopoietic recovery (ANC was ≥ 0.5 × 10^9/L for three consecutive days, and then declined to below 0.5 × 10^9/L for at least three consecutive days). A subsequent autologous HCT for graft failure or rejection does not require an additional Pre-TED (Form 2400) or Baseline (2000) to be completed.
- **Persistent primary disease.** Additional stem cells are required because of the persistent presence of disease pre and post transplant (i.e., complete remission was never achieved following the previous transplant).
- **Recurrent primary disease.** Additional stem cells are required because of relapsed primary disease (i.e., complete remission was achieved pre or post transplant, but the disease relapsed following the previous transplant).
- **Planned second HCT, per protocol.** Additional stem cells are given as defined by the protocol for a subsequent transplant/infusion. This transplant is not based upon recovery, disease status, or any other assessment.
- **New malignancy (including PTLD and EBV lymphoma).** Additional stem cells are required because the recipient has developed a new malignancy. This does not include a transformation or progression of the original malignancy for which the recipient was transplanted (refer to question 131 for more information). If “new malignancy” is selected, also complete questions 131-173.
- **Stable, mixed chimerism.** Mixed chimerism is the concurrent presence of donor and recipient hematopoietic cells. Stable mixed chimerism indicates the quantity of donor/recipient hematopoietic cells is neither going up nor down. In the case of a stable, mixed donor chimerism, the infusion of additional cells (usually lymphocytes and not mobilized stem cells) is typically classified as a DCI. Verify with the transplant physician that the cells given should be reported as a subsequent transplant and that stable, mixed chimerism is the reason for the transplant.
- **Declining chimerism.** In the case of declining chimerism—when the percentage of donor cells is decreasing on several sequential studies, indicating possible impending graft failure—additional stem cells are required. Usually the donor chimerism has fallen below 30-50%.
- **Other.** If additional stem cells are given for a reason other than the options listed, select “other” and complete question 220.

Multiple Products

In the FormsNet3^{SM} application, use the multiple feature to complete questions 221-223 for each product infused. For paper form submission, copy and complete questions 221-223 for each product infused.

Questions 221-223: Source of HSCs

Report the stem cell source of the recipient's subsequent HCT.

If "allogeneic, related" is selected, indicate whether the same donor was used in question 222 and complete a new Pre-TED Form (2400) and Recipient Baseline Data Form (Form 2000).

If "allogeneic, unrelated" is selected, specify the product/donor type in question 223 and complete a new Pre-TED Form (2400) and Recipient Baseline Data Form (Form 2000).

If "autologous" is selected, complete a new Pre-TED Form (2400) and Recipient Baseline Data Form (Form 2000)., unless the indication for transplant was due to engraftment reasons (indications 1-3 in question 219).

Q224-332: Donor Cellular Infusion (DCI) Information

This section captures information on DCIs (question 5, answered “yes”) from any donor source (unstimulated peripheral blood mononuclear cells, T cells, NK cells, other cells). Complete this DCI section for all infusions given in a 10 week period. If the recipient did not receive any DCIs, continue with the signature lines.

For information on how to distinguish infusion types (e.g., HCT versus DCI), see Appendix O.

Additional information regarding DCIs is available on the CIBMTR website: http://www.cibmtr.org/Meetings/Materials/CRPDMC/index.html

The paper version of the Greater Than Two Year Post-HCT Data Form (2300) provides space to report one Donor Cellular Infusion (DCI) event (in a 10-week period). If more than 10 weeks have elapsed between DCIs, copy and complete this section for each 10-week period. The FormsNet3^{SM} application will allow as many DCI entries as needed.

A DCI is a form of immunotherapy that is commonly used to treat infections (e.g., viral) or recurrent disease. In the setting of recurrent disease, the DCI is used to create a graft-versus-leukemia/tumor (GVL/GVT) effect. A DCI may also be utilized to treat GVHD or promote engraftment when chimerism studies reveal less than 100% donor cells. The recipient does not receive a preparative regimen prior to receiving the additional donor cells since replacement of the marrow is not the goal.

A DCI should not be reported if additional donor cells are given for failed ANC recovery, partial or poor ANC recovery, loss of graft, or late graft failure. These would be considered as subsequent HCTs.

The types of cells used for a DCI include, but are not limited to the following:

- Lymphocytes (TC – T Cells): A therapeutic product from any source containing a quantified T-cell population.
- Peripheral blood mononuclear cells (both stimulated and unstimulated) (TC – Whole Blood): Whole blood collected as a source of nucleated cells intended for therapeutic use other than HPCs.
- Dendritic cells from the original donor (TC – DC): A therapeutic cell product containing dendritic cells for therapeutic use.
- Mesenchymal cells (TC – MSC): A therapeutic product containing mesenchymal stromal cells for therapeutic use.

Recipients may receive DCI infusions over several days or weeks. A single DCI section should be completed for all infusions given within a 10-week period.

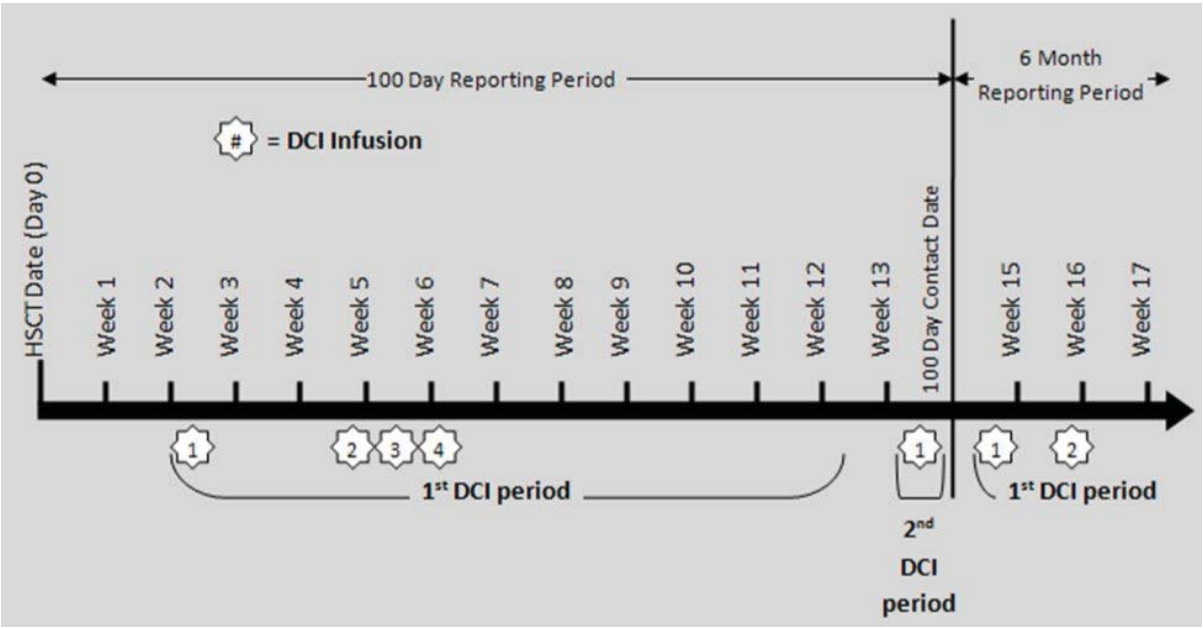
Complete the first DCI section for all infusions given between day 0 (of the DCI) and 10 weeks post initial DCI infusion. If the recipient receives an additional DCI, but it is infused after the initial 10-week period, report this subsequent DCI in a second DCI section. Any additional infusion(s) performed within 10 weeks of DCI should be reported in the subsequent DCI section.

This 10-week period is limited to within a reporting period; if the recipient continues to receive infusions beyond the 100 Day date of contact, report infusions only until the contact date (even if the period has not yet extended 10 weeks since the initial infusion). Report the first DCI in the new reporting period (Form 2200) under the first DCI instance and begin the 10-week reporting period again.

In this example, four DCIs are reported in the first 10-week period and one DCI is reported in the second 10-week period within the 100-day reporting period (which ends at the 100 Day contact date). At least two DCIs would be reported in the first DCI instance in the six-month reporting period.

See the illustration below for an example of a recipient receiving multiple DCIs.

Example: Calculation Timeline



Question 224: Date the first DCI was given

Report the date of the recipient's first DCI given in this reporting period.

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

Question 225: Specify the number of cell infusions given within 10 weeks of the first DCI

Indicate the total number of DCIs given in a 10-week period or up to the date of contact, whichever comes first. (In Example 1, the total number is four).

Question 226: Was the DCI infusion performed at a different institution?

Indicate if the DCI was performed at another institution. If “yes,” continue with question 227. If “no,” continue with question 228.

Question 227: Specify the institution that performed the DCI

Report the name, city, state, and country of the institution where the recipient’s DCI was performed. These data are used to identify and link the recipient’s existence in the database.

Question 228: Indication for DCI

Indicate the reason for the DCI. If multiple DCIs were given within the 10-week period, select the most appropriate reason in the FormsNet3 application. If completing the paper version of the form, check all applicable indications.

- **Planned as part of initial HCT protocol.** Additional cells are given because the protocol planned for a DCI. This infusion is not based upon hematopoietic recovery, disease status, or any other assessment.
- **Treatment for relapsed, persistent, or progressive disease.** Following the HCT, additional cells were given because:
    - The disease for which the recipient was transplanted relapsed.
    - The recipient was transplanted with disease present and never entered a remission.
    - The disease for which the recipient was transplanted has progressed.

  If the reason for treatment is relapsed, persistent, or progressive disease, also complete questions 229-236.

- **Treatment for B cell lymphoproliferative disorder (PTLD, EBV lymphoma).** Additional cells are given because the recipient developed a B cell lymphoproliferative disorder such as PTLD or EBV lymphoma.
- **Treatment for GVHD.** Mesenchymal cells are given as treatment for GVHD.

- **Viral Infection.** Additional cells (example: T-lymphocytes) are given because the recipient developed a viral infection. If the reason is viral infection, also complete question 237.
- **Stable, mixed chimerism.** Mixed chimerism is the concurrent presence of donor and recipient hematopoietic cells. Stable mixed chimerism indicates the quantity is neither going up nor down. Lymphocytes may be infused to reduce and potentially eliminate the host cells and improve donor cell percentage.
  If the reason is stable, mixed chimerism, also complete question 238. If multiple chimerism tests were performed in the reporting period, document the date the stable, mixed chimerism was first detected.
- **Loss of/decreased donor T-cell chimerism.** In the case of declining chimerism, when the percentage of donor cells is sequentially decreasing on several studies (indicating possible impending graft failure), additional cells are required. Usually the donor chimerism has fallen below 30-50%. The purpose of the infusion of donor T-cells is to restore 100% donor chimerism.
  If the reason for the DCI is loss of/decreased donor T-cell chimerism, also complete question 238. If multiple chimerism tests were performed in the reporting period, document the date the loss of/decreased T-cell chimerism was first detected.
- **Other.** Additional cells are required and/or given for a reason other than the options listed. If the DCI is for another reason, select “other” and complete question 239.

Question 229-234: Specify the method(s) of disease detection below

If the reason for the DCI is treatment for relapsed, persistent, or progressive disease, indicate the method(s) of disease detection. For each method used, if the result was positive, report the first date the disease was detected. If the result was negative, report the last method date prior to the DCI date (question 224).

Questions 235-236: Was chemotherapy used to attempt to induce disease response prior to the first DCI?

If the reason for the DCI is treatment for relapsed, persistent, or progressive disease, indicate whether chemotherapy was used to attempt to induce disease response prior to the DCI. If “yes,” continue with question 236 and report the date of administration of the final chemotherapy dose. If “no,” continue with question 240.

Question 240: What was the recipient’s disease status immediately prior to the first DCI?

When determining disease status, refer to the Pre-TED Form Instructions for the specific definitions for each disease. Indicate the recipient’s disease status immediately prior to the first DCI. If the recipient’s disease status was not evaluated post-HCT, select “not evaluated post-HCT,” and continue with question 242.

Question 241: Date disease status was established prior to the first DCI

Report the date of the most recent assessment (e.g., pathology, radiology, laboratory, physician assessment) prior to the first DCI. Enter the date the sample was collected for examination, the date the radiological examination was performed, or the date the disease was assessed by a physician.

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

Question 242: Specify the functional status of the recipient immediately prior to the first DCI

The Karnofsky Scale is designed for recipients aged 16 years and older, and is not appropriate for children under the age of 16. The Lansky Scale is designed for recipients less than 16 years old.

Recipient performance status is a critical data field that has been determined to be essential for all outcome-based studies. Determination of performance status is ideally performed by a healthcare provider. Centers are encouraged to put tools in place to facilitate this collection. If a Karnofsky/Lansky score is not documented in the source documentation (e.g., inpatient progress note, physician's clinic note), data professionals are encouraged to discuss a determination with the healthcare provider rather than make an assignment themselves that may be based on inadequate information. The CIBMTR recognizes that some transplant centers prefer to assign and use the ECOG performance score as opposed to the Karnofsky/Lansky score. Although the ECOG and Karnofsky/Lansky performance score systems are based on similar principles, the scales are not the same. For example, the Karnofsky/Lansky scale is described in 10 categories, whereas the ECOG performance status is reported in six categories. Due to the overlap between the two systems, an ECOG score of "one" can represent either "80" or "90" on the Karnofsky/Lansky scale; whereas, a Karnofsky/Lansky score of "80" or "90" is converted directly to an ECOG score of "one." Therefore, the Karnofsky/Lansky scale can be more accurately converted into ECOG.

However, for centers that collect only an ECOG performance score, CIBMTR will make the following accommodations when auditing the source data:

- Centers assigning ECOG scores should do so using standard practices to ensure accuracy.
- For the purposes of CIBMTR reporting, conversion of ECOG to Karnofsky/Lansky should follow a standard and consistent practice to account for the lack of direct mapping. This practice should be clear and reproducible.

Indicate the score (10-100) that best represents the recipient's activity status immediately prior to the first DCI. The only valid scores are 10-100, zero is not a valid response for this scale, nor are values not ending in zero, such as "85." The Karnofsky/Lansky scale can be found in Appendix L.

Questions 243-249: Specify DCI source

Indicate the source of the cells used for the DCI as:

- Collected at the time of PBSC mobilization and collection.
- Negative fraction of CD34 selected PBSC.
- Negative fraction of CD34 selected bone marrow.
- Apheresis at a different time than collection of PBSC used for allogeneic HCT. If “yes,” specify the date of apheresis in question 247.
- Isolated from a unit(s) of whole blood. If “yes,” specify the number of units in question 249.

Question 250: Were the donor cells collected by leukapheresis?

Leukapheresis is a procedure in which white blood cells are removed from the donor and portions are used for the DCI. Indicate whether the donor cells for the DCI were collected by leukapheresis. If “yes,” continue with question 251. If “no,” continue with question 254.

Question 251: Date of first leukapheresis

Report the date of the first leukapheresis.

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

Question 252: Date of last leukapheresis

Report the date of the last leukapheresis.

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

Question 253: Number of leukaphereses

Report the number of leukapheresis procedures.

Question 254: Did the donor receive treatment to enhance cell collection prior to donation?

Stem cells do not typically circulate in the blood stream. Therefore, in order to increase the quantity of cells for collection, an agent is frequently given to the allogeneic donor or autologous recipient. The purpose of the agent is to move the stem cells from the bone marrow into the peripheral blood. This practice is often referred to as mobilization or priming. In general, mobilization or priming is not required to collect a DCI

product when it is isolated from whole blood or by apheresis at a different time than collection of PBSCs used for allogeneic HCT. Indicate whether the donor received treatment to enhance cell collection prior to donation. If “yes,” continue with question 255. If “no,” continue with question 262.

Question 255-261: Specify treatment(s) given

- **G-CSF (granulocyte colony-stimulating factor).** Indicate if the donor/autologous recipient received G-CSF (filgrastim, Neupogen®) prior to the cell harvest to enhance the product.
- **GM-CSF (granulocyte-macrophage colony-stimulating factor).** Indicate if the donor/autologous recipient received GM-CSF (sargramostim, Leukine®) prior to the cell harvest to enhance the product.
- **Other (growth factor).** If the donor/autologous recipient received a growth factor such as AMD3100 (plerixafor, Mozobil®) prior to the cell harvest, check “yes” and specify the other growth factor(s) given to the donor/autologous recipient in question 259.
- **Other treatment.** If the donor/autologous recipient received any other treatment prior to the cell harvest to enhance the product, check “yes” and specify the other treatment administered to the donor/autologous recipient in question 261.

Questions 262-268: For each DCI given, report the total number of cells infused.

Report the total number of cells infused and specify the exponent for each cell type. If the cells were cryopreserved, report the totals after processing, but before cryopreservation. If multiple cellular infusions were given within the 10-week period, report the cumulative total of all cells infused; submit a log of appended documents showing the product analyses for each individual DCI product.

Question 269: Were dendritic cells infused?

Indicate whether dendritic cells were infused.

Question 270: Were fibroblasts infused?

Indicate whether fibroblasts were infused.

Questions 271-272: Were any other cell types infused (not including cell types reported in questions 262-268)?

Indicate whether any other cell types were infused. If “yes,” specify the cell type in question 272.

Question 273: Were the cells cryopreserved prior to infusion?

Indicate whether the cells were cryopreserved prior to infusion. If “yes,” continue with question 274. If “no,” continue with question 275.

Question 274: Specify portion cryopreserved

Specify whether all of the cells or a portion of the cells were cryopreserved prior to infusion.

Product Manipulation
Cryopreservation is not considered a method of product manipulation. If the product was cryopreserved, but no actual manipulation was performed, report “no” for question 275.

Question 275: Were the cells manipulated prior to infusion?

If any part of the product was manipulated in any way prior to infusion, check “yes” and continue with question 276. **Do not report cryopreservation as a method of manipulation.** If the product was not manipulated, check “no” and continue with the signature lines.

Question 276: Specify portion manipulated

If all of the cells were manipulated using the same method, select “all cells.” If some of the cells were manipulated, select “portion of cells.”

Report all methods used to manipulate the product at the transplant facility only (i.e., if the product was shipped to your facility, do not report manipulation of the product that was performed at the collection center).
All bags from one mobilization cycle are considered a single product; report all manipulation methods used on any part of the single product.
Do not report methods of manipulation performed as part of another procedure (e.g., T-cell depletion as part of expansion).

Plasma Removal versus Volume Reduction
Plasma removal for ABO incompatibility (question 281) is performed for ABO or Rh incompatibility between the donor and recipient. Volume reduction as a manipulation method (question 288) is performed for the sole purpose of reducing the total volume of product (not as a result of any incompatibility between the donor and recipient).
If “yes” is reported for both question 281 and 288, the product must be plasma reduced for ABO incompatibility and then further reduced to decrease the total product volume.

Question 277: ABO incompatibility

RBC or plasma depletion is often used in cases where there is ABO incompatibility between donor and recipient. Incompatibility can cause hemolysis and delayed red blood cell recovery.

This option should be used for **allogeneic** products only; report RBC depletion of **autologous** products as "volume reduction" under question 288. Indicate if the product was manipulated for ABO incompatibility. If "yes," continue with question 278. If "no," continue with question 285.

Questions 278-284: Specify method

Indicate the method(s) used for ABO incompatibility manipulation. If "other" is selected, specify the method in question 284.

Question 285: Dextran-albumin wash

A dextran-albumin wash method is used to improve cell recovery and reduce reaction(s) to the infusion.

Indicate if a dextran-albumin wash method was used on the product.

Question 286: Ex-vivo expansion

Ex-vivo expansion is a type of manipulation where the cells have been maintained ex vivo (cultured) to activate, expand, or promote development of a specified cell population in the presence of specified additive(s). The most common method of ex vivo expansion uses hematopoietic growth factors. Ex-vivo expansion is most commonly used with cord blood transplants.

Indicate if ex-vivo expansion was used on the product. Do not report T-cell depletion separately if it was done as a part of this procedure.

Question 287: Genetic manipulation (gene transfer/transduction)

Genetic manipulation (gene transfer/transduction) may be used to lessen the negative effects of DCIs. For example, a DCI may include T cells that have been transduced with HSV-TK (herpes simplex virus) that are susceptible to gancyclovir treatment. A recipient who develops DCI-related GVHD may be treated effectively with gancyclovir.

Indicate if genetic manipulation was used on the product.

Question 288: Volume reduction

The purpose of volume reduction is specifically to reduce the volume in order to prevent volume overload. Indicate if volume reduction was used to manipulate the product.

Question 289: CD34+ selection

CD34+ selection is a manipulation method also known as “positive selection.” This method intensifies and selects stem cells that have a CD34+ marker on the cell surface, and is commonly done with a CliniMACS®/CliniMax or Isolex® machine.

Indicate if CD34+ selection was used. If “yes,” continue with question 290. If “no,” continue with question 292.

Questions 290-291: Specify manufacturer of CD34+ selection machine

Indicate the type of machine used for CD34+ selection. If “other” is selected, specify the manufacturer in question 291.

Questions 292-302: T-cell depletion

This method of negative selection manipulation is most commonly used for allogeneic HCT, as it removes some or all of the T cells in an effort to minimize GVHD. The removed T-cells may be infused at a later date (e.g., DCI). Methods of T-cell depletion may include the use of antibodies.

Indicate if the product was T-cell depleted and the method used. If “yes” is selected for questions 293-298, indicate the specific antibodies used for T-cell depletion in questions 305-322. If “other” is selected, specify the method in question 302.

Questions 303-304: Other cell manipulation

Indicate if the cells were manipulated using any other method, and specify the manipulation type in question 304.

Examples include but are not limited to the following:

- Preparation of T regulatory cells
- B-cell reduction
- Buffy coat enrichment
- CD133 enrichment
- Monocyte enrichment
- Mononuclear cell enrichment
- PUV treatment

Cryopreservation is NOT considered a method of manipulation. Do not include cryopreservation or freeze media in the “other cell manipulation” category.

Question 305: Were antibodies used during graft manipulation?

If antibodies were used during product manipulation, select “yes” and continue with question 306. If antibodies were not used, select “no” and continue with the signature lines.

Questions 306-322: Specify antibodies

Specify whether each antibody listed was used for product manipulation. Do not leave any responses blank. If “other CD3” is selected, specify what in question 316. If “Anti CD52” is selected, further specify the antibody in questions 318-320. If “other antibody” is selected, specify in question 322.