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

Question 131: 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 132: 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 133: 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 134: Diagnosis was based on

Select the method used to diagnose chronic GVHD.

Question 135: 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 136: 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.

Select the overall severity of chronic GVHD.

Questions 137-166: 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 Bronchiolitis Obliterans section, questions 262-270**.
- Other pulmonary involvement: include related pulmonary disorders here. Do not report interstitial pneumonitis (IPn). Report IPn in the Pulmonary Function section, questions 239-260.

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 165.

Questions 167-197: Was specific therapy used to treat chronic GVHD?

Indicate whether therapy was used to treat chronic GVHD. If "yes," continue with question 168. If "no," continue with question 198.

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 102-128 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 given by mouth for treatment of gut GVHD, but 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 196-197).

Question 198: 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 1). 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 199: 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 200. If “yes” or “unknown,” continue with question 201.

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 200: 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.

Q201-237: Infection

Infection Prophylaxis
It is important to look at the Medication Administration Record (MAR) throughout the entire reporting period, as one prophylactic drug may be stopped due to a reaction, while another will be started in its place. Also, the use of some infection prophylactic drugs may not start immediately post-HCT (example: pentamidine).

Questions 201-230: Did the recipient receive any of the following agents for infection prophylaxis since the date of the last report?

Indicate whether specific antimicrobial therapy to prevent infections was administered within the reporting period. Most transplant centers have specific infection prophylaxis protocols that may include: antiviral, antifungal, antibacterial, and/or anti-*PCP* drugs. Any agents a recipient received as a result of these protocols should be included in this section.

Report prophylactic immunoglobulins in the Immune Reconstitution section (questions 34-35).

Do not report agents used as treatment for documented or suspected infections.

If “yes,” continue with question 202. If “no” or “unknown,” continue with question 231. For each agent listed, indicate whether it was used to prevent infection.

Systemic antibacterial antibiotics:
These agents may be given IV (example: ceftazadime) or orally (example: ciprofloxacin).

Non-absorbable oral antibiotics:
The main purpose of these agents is to sterilize the gastrointestinal tract. Examples include: Coly-Mycin® S, colistin sulfate, polymixin E, Mycifradin®, Neobiotic®, neomycin, Aerosporin, polymyxin B.

If “other systemic antifungal agent,” “other antiviral agent,” “other pneumocystis prophylaxis,” or “other prophylaxis agent” is selected, specify the agent given.

Questions 231-235: Did the recipient develop a clinically significant infection since the date of the last report?

Indicate if 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 (exceptions: oral thrush, toe nail fungus, etc.). Surveillance cultures in which normal flora is present and the recipient is asymptomatic do not need to be reported.

Report interstitial pneumonitis (IPn that developed from an infection, (CMV, adenovirus, etc) in the Pulmonary Function section (questions 239-260).

If “yes,” continue with question 232. If “no,” continue with question 236.

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

Organism: From the drop down menu, select the code corresponding to the identified or suspected organism as reported on the microbiology, laboratory report, or other physician documentation. Report the code in the boxes provided. If the specific organism is not listed, use the “other, specify” code (198 – bacteria, 209 – candida, 219 – aspergillus, 259 – fungus, 329 – virus, 409 – parasite) and report the name of the organism in the space provided. If an organism is suspected, but not identified, report using codes 501-505, as applicable. If the source of the infection is not identified, use code 509.

Bacterial infections: *Atypical bacteria* (codes 101-119 and 501) are collected separately from other more common types of bacteria. *Typical bacteria* are codes 120-198 and 502. If more than one typical bacterial organism is found in a single site, include all the organisms in one listing; do not record each separately. Either write the code in the margin or use Report “Notes.”

Fungal infections: Note the inclusion of Pneumocystis (formerly found under parasites). The most commonly found fungal infections are Candida (*C. albicans, C. tropicalis, C. glabrata* [also known as *Torulopsis glabrata*], *C. parapsilosis, C. krusei*), *Aspergillus (A. fumigatus), Fusarium sp*., and *Zygomycetes*.

- For fungal species marked with a section symbol (§), also complete a Fungal Infection Form (2146).

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

- For hepatitis infections marked with a dagger symbol (†), also complete a Hepatitis Form (2147).
- For HIV infections marked with a currency symbol (¤), also complete an HIV Infection Form (2148).

Parasitic infections: These are fairly rare. Toxoplasma gondii is often transmitted through the handling of cat litter. Giardia and Cryptosporidium can be found in contaminated water.

Fever of undetermined origin: Defined as any fever (> 38°C) not associated with documented/suspected infection in a specific site, these are not collected by the CIBMTR because the occurrence is too common for analysis.

Site: From the drop down menu, select the code corresponding to the site of the infection. If three or more sites are infected with the same organism, enter code 2 (Disseminated- generalized, isolated at 3 or more distinct sites).

Disseminated Infections
The CIBMTR acknowledges that a discrepancy exists between the CIBMTR definition (3 or more sites) and the BMT CTN definition (2 or more sites) for disseminated infections.

Date of Diagnosis: Report the date of diagnosis of the infection as the collection date for the positive microbiology culture. For suspected infections, enter the date of a radiological test or the date treatment was started as the date of diagnosis.

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

Questions 236-237: Did the recipient develop more than 7 infections post-HCT?

Indicate whether the recipient developed more than seven infections post-HCT.

If “yes,” use the multiple feature to report the organism, site, and date of diagnosis for each infection in the FormsNet3SM application. For paper form submission, make a copy of the Infection section to report multiple infections and indicate that extra pages are attached.

If “no,” continue with question 238.

Bacterial Infections: If the infection is due to bacteria (except for Clostridium difficile), and recurs in less than or equal to 7 days off antimicrobial therapy, it is considered a single incident and should *not* be reported multiple times.

- **Example:** In the case of VRE, where antibiotic (i.e., Linezolid) therapy can last 14-28 days, the recipient would have to be off antibiotics for more than 7 days to report a new VRE infection of the same site again.

If the infection is due to Clostridium difficile, and recurs in less than or equal to 30 days, it is considered a single incident and should *not* be reported multiple times.

If the infection is due to Helicobacter pylori, and recurs in less than or equal to 365 days, it is considered a single incident and should *not* be reported multiple times.

Viral Infections: If the infection is due to VZV, HZV, Adenovirus, Enterovirus, Influenza, Parainfluenza or Rhinovirus, and recurs in less than or equal to 14 days, it is considered a single incident and should *not* be reported multiple times.

If the infection is due to CMV, HSV, EBV, HHV-6 or Polyomavirus (BK virus), and recurs in ≤ 60 days, it is considered a single incident and should *not* be reported multiple times.

Fungal Infections: If the infection is due to yeast (e.g., Candida), and recurs in ≤ 14 days, it is considered a single incident and should *not* be reported multiple times.

If the infection is due to mold (e.g., aspergillus), and recurs in ≤ 90 days, it is considered a single incident and should *not* be reported multiple times.

Q238-389: Organ Function

Pulmonary Function

Bacterial and Fungal Pneumonia:
Report bacterial and fungal pneumonia in Infection section (questions 231-235).

Question 238: Did the recipient develop interstitial pneumonitis (IPn), or ARDS) and/or idiopathic pneumonia syndrome (IPS) since the date of the last report?

Interstitial pneumonitis or Acute Respiratory Distress Syndrome (ARDS) can result from infectious or non-infectious causes. Infectious causes may be bacterial, viral (CMV, adenovirus, respiratory syncytial virus [RSV], influenza, etc.), or fungal. Interstitial pneumonitis may also be idiopathic (no organism was isolated).

Idiopathic pneumonia syndrome defines **all non-infectious lung** injuries that occur early after HCT (within 100-120 days) including: peri-engraftment respiratory distress syndrome (PERDS), interstitial pneumonitis without a pathogen, radiation/drug-induced lung injury, or transfusion-associated lung injury (TRALI).

Diagnostic methods for IPn, ARDS, and/or IPS include x-ray, bronchoscopy (including bronchoalveolar lavage), biopsies, arterial blood gas assessments, CBC, blood chemistries, and cultures.

If “yes,” continue with question 239. If “no,” continue with question 261.

Question 239: Date of diagnosis of IPn / IPS

Report the date of diagnosis of IPn/IPS. 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.

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

Question 240: Were diagnostic tests done (other than radiographic studies)?

In addition to radiographic studies used to determine evidence of IPn/IPS, indicate whether diagnostic tests were performed. If “yes,” continue with question 241. If “no,” continue with question 247.

Question 241-246: Diagnosis was evaluated by

Select the method used for diagnosis of IPn/IPS. If “other test” is selected, specify the test method used in question 246.

Bronchoalveolar lavage (BAL): a procedure in which a bronchoscope is guided into the lower respiratory system. Fluid is emitted from the bronchoscope and then collected for further examination.
Transbronchial biopsy: a procedure in which forceps on the end of the bronchoscope are used to collect lung tissue samples for further examination.
Open/Thorascopic (video-assisted thoracoscopic surgery [VATS]) lung biopsy: An open lung biopsy is a procedure in which an incision is made between the ribs to collect a sample of lung tissue for further examination. A thorascopic lung biopsy is a procedure in which an incision is made to the chest and an endoscope is used to collect samples of lung tissue.
Autopsy: a post-mortem procedure used to determine the cause of death and to evaluate other disease present at the time of death.
Other: report other evaluations for IPn, ARDS or IPS in question 246, excluding radiographic assessment.

Question 247: Was an organism isolated?

If an organism was isolated, check “yes,” and continue with question 248. If an organism was not isolated, the cause was non-infectious or idiopathic, or the organism isolated was thought to be a contaminant, check “no,” and continue with question 259.

Questions 248-258: Etiology

Indicate “yes” or “no” for each organism isolated. If “other virus” is selected, specify the virus isolated in question 256. If “other organism” is selected, specify the organism isolated in question 258.

Question 259-260: Did the recipient experience two or more episodes of IPn / IPS since the date of the last report?

Indicate whether the recipient developed two or more episodes of IPn/IPS during this reporting period. If the etiology of IPn is infectious, use the timelines provided for infections under question 236 of the Infection section above to determine if multiple episodes of infectious IPn occurred. If the etiology is non-infectious, a recipient must have completed steroid treatment or been weaned from prednisone to adrenal level dosing (≤ 20 mg/day) before reporting the development of a subsequent episode of IPS. If “yes,” complete questions 238-260 for each infection in the FormsNet3SM application. For paper form submission, make a copy of the Pulmonary Function section to report multiple infections and indicate that extra pages are attached.

Question 261: Did the recipient develop non-infectious pulmonary abnormalities (other than IPn / IPS / ARDS) since the date of the last report?

Indicate whether the recipient developed a non-infectious pulmonary abnormality since the date of last report. If “yes,” continue with question 262. If “no,” continue with question 291.

Non-infectious pulmonary abnormalities include but are not limited to: diffuse alveolar hemorrhage (DAH), bronchiolitis obliterans (BO/BOS), and bronchiolitis obliterans with organizing pneumonia (BOOP)/cryptogenic organizing pneumonia (COP).

Bronchiolitis Obliterans (BO) and Bronchiolitis Obliterans with Organizing Pneumonia (BOOP)
Both BO and BOOP are pulmonary complications that occur late after HCT (in contrast to IPS, which occurs early post-HCT). BO is an obstructive complication that affects the small airways. BOOP is a restrictive complication that affects the alveoli ducts and alveoli (air sacs). Idiopathic BOOP is also known as cryptogenic organizing pneumonia (COP).

Question 262: Did the recipient develop bronchiolitis obliterans since the date of the last report?

Bronchiolitis obliterans is often a manifestation of chronic GVHD. Check to see if the recipient has either histological or clinical evidence of chronic GVHD of the lung. If bronchiolitis obliterans is a result of chronic GVHD, confirm that chronic GVHD of the lung was documented on this form (question 145).

Indicate whether the recipient developed bronchiolitis obliterans since the date of the last report. If “yes,” continue with question 263. If “no,” continue with question 271.

Question 263: Date of diagnosis

Report the date of diagnosis of bronchiolitis obliterans.

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

Question 264: Were diagnostic tests done?

Indicate whether diagnostic tests were performed. If “yes,” continue with question 265. If “no” continue with question 271.

Bronchiolitis obliterans is mainly diagnosed using pulmonary function tests (PFT) that show airway obstruction.

Question 265-270: Diagnosis was evaluated by

Select the method used for diagnosis of bronchiolitis obliterans. If “other test” is selected, specify the test method used in question 270.

Bronchoalveolar lavage (BAL): a procedure in which a bronchoscope is guided into the lower respiratory system. Fluid is emitted from the bronchoscope and then collected for further examination.
Transbronchial biopsy: a procedure in which forceps on the end of the bronchoscope are used to collect lung tissue samples for further examination.
Open/Thorascopic(video-assisted thoracoscopic surgery [VATS]) lung biopsy: An open lung biopsy is a procedure in which an incision is made between the ribs to collect a sample of lung tissue for further examination. A thorascopic lung biopsy is a procedure in which an incision is made in the chest and an endoscope is used to collect samples of lung tissue.
Autopsy: a post-mortem procedure used to determine the cause of death and to evaluate other disease present at the time of death.
Other: report other evaluations for BO in question 270.

If PFT and/or radiographic imaging are used to diagnose BO in the absence of lung biopsy, select “other test” and specify PFT and/or radiographic imaging in question 270.

Question 271: Did the recipient develop pulmonary hemorrhage?

Indicate whether the recipient developed a pulmonary hemorrhage, including diffuse alveolar hemorrhage (DAH), since the date of the last report. If “yes,” continue with question 272. If “no,” continue with question 280.

Question 272: Date of diagnosis

Report the date of diagnosis of pulmonary hemorrhage. 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.

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

Question 273: Were diagnostic tests done?

Indicate whether diagnostic tests were performed. If “yes,” continue with question 274. If “no,” continue with question 280.

Question 274-279: Diagnosis was evaluated by

Select the method used for diagnosis of pulmonary hemorrhage. If “other test” is selected, specify the test method used in question 279.

Bronchoalveolar lavage (BAL): a procedure in which a bronchoscope is guided into the lower respiratory system. Fluid is emitted from the bronchoscope and then collected for further examination.
Transbronchial biopsy: a procedure in which forceps on the end of the bronchoscope are used to collect lung tissue samples for further examination.
Open/Thorascopic (video-assisted thoracoscopic surgery [VATS]) lung biopsy: a procedure in which an incision is made between the ribs to collect a sample of lung tissue for further examination. A thorascopic lung biopsy is a procedure in which an incision is made in the chest and an endoscope is used to collect samples of lung tissue.
Autopsy: a post-mortem procedure used to determine the cause of death and to evaluate other disease present at the time of death.
Other: report other evaluations for pulmonary hemorrhage in question 279.

Question 280: Did the recipient develop cryptogenic organizing pneumonia (COP)?

Cryptogenic organizing pneumonia is also known as bronchiolitis obliterans with organizing pneumonia (BOOP). Indicate whether the recipient developed cryptogenic organizing pneumonia or BOOP since the date of the last report. If “yes,” continue with question 281. If “no,” continue with question 289.

Question 281: Date of diagnosis

Report the date of diagnosis of cryptogenic organizing pneumonia. 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.

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

Question 282: Were diagnostic tests done?

Indicate whether diagnostic tests were performed. If “yes,” continue with question 283. If “no,” continue with question 289.

Question 283-288: Diagnosis was evaluated by

Select the method used for diagnosis of cryptogenic organizing pneumonia. If “other test” is selected, specify the test method used in question 288.

Bronchoalveolar lavage (BAL): a procedure in which a bronchoscope is guided into the lower respiratory system. Fluid is emitted from the bronchoscope and then collected for further examination.
Transbronchial biopsy: a procedure in which forceps on the end of the bronchoscope are used to collect lung tissue samples for further examination.
Open/Thorascopic (video-assisted thoracoscopic surgery [VATS]) lung biopsy: a procedure in which an incision is made between the ribs to collect a sample of lung tissue for further examination. A thorascopic lung biopsy is a procedure in which an incision is made in the chest and an endoscope is used to collect samples of lung tissue.
Autopsy: a post-mortem procedure used to determine the cause of death and to evaluate other disease present at the time of death.
Other: report other evaluations for COP in question 288.

Questions 289-290: Did the recipient develop any other non-infectious pulmonary abnormalities?

Indicate whether the recipient developed any other non-infectious pulmonary abnormality since the date of the last report. If “yes,” specify the other pulmonary abnormality in question 290. If “no,” continue with question 291.

Question 291: Did the recipient receive endotracheal intubation or mechanical ventilation since the date of the last report?

Endotracheal intubation or mechanical ventilation may be used post-HCT for respiratory failure or for airway protection from severe mucositis.

Invasive positive pressure ventilation is delivered via an endotracheal tube. Do not include non-invasive positive pressure ventilation that is delivered through an alternate interface (e.g., facemask).

Indicate whether the recipient received endotracheal intubation or mechanical ventilation (invasive positive pressure ventilation) post-HCT.

Liver Function

Liver Toxicity:
Questions 292-314 are designed to collect information on the level of liver dysfunction that is not related to acute or chronic GVHD (example: chemotoxicity, cyclosporine toxicity, veno-occlusive disease [VOD]). Liver dysfunction secondary to causes other than GVHD may be determined by biopsy, viral culture, or suspected by clinical evidence.

Question 292: Did the recipient develop non-infectious liver toxicity (excluding GVHD) since the date of the last report?

Cirrhosis: degenerative liver disease in which fibrous tissue forms and the lobes become filled with fat.
Hepatic veno-occlusive disease (VOD): can be caused by systemic chemotherapy or radiation therapy. VOD consists of endothelial damage, micro thrombosis of the hepatic venules, and sinusoidal fibrosis. It is more common in allogeneic transplants than autologous and typically occurs within 3 weeks of transplant. In the absence of a histological diagnosis, recipients must fulfill the following criteria for a diagnosis of VOD (McDonald GB, et al. *Hepatology* 1984; 4:226-112. Jones RJ, et al. *Transplantation* 1987; 778-783.):

- Jaundice (bilirubin ≥ 2 mg/dL or > 34 µmol/L)
- Hepatomegaly with right upper quadrant pain
- Ascites and/or weight gain

Other: report liver abnormalities not listed above. Do not include hepatic infections or GVHD. Report infections in the Infection section (questions 231-235) and GVHD in the Acute (questions 81-128) and/or Chronic (questions 129-200) GHVD sections.

Indicate whether the recipient developed a non-infectious liver toxicity since the date of the last report. If “yes,” continue with question 293. If “no,” continue with question 315.

Question 293: Date of diagnosis

Report the date of diagnosis of non-infectious liver toxicity. The clinical diagnosis date may not necessarily be the date the symptoms began (example: the recipient developed ascites prior to the physician’s documenting clinical evidence of veno-occlusive disease). If the diagnosis is based on histological, radiological, hematologic, or other methods, report the date of specimen collection. 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.

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

Questions 294-302: Etiology

For each option listed, indicate whether it was the cause of the recipient’s liver toxicity and, if applicable, answer any additional questions. If “other” is selected, specify the cause in question 301.

Questions 303-314: Specify diagnosis of liver toxicity by clinical signs and symptoms/evaluation

For each sign, symptom, or evaluation listed, indicate whether it was used to diagnose the recipient's liver toxicity. If "other" is selected, specify the evaluation in question 314.

Ascites: the accumulation of fluid in the abdomen that ranges from mild to severe. Diagnosis may be made by clinical evaluation, laboratory tests, and/or radiological imaging.
Autopsy: a post-mortem procedure used to determine the cause of death and to evaluate other disease present at the time of death.
Bilirubin > 2.0 mg: elevated bilirubin may be a sign of liver toxicity, but clinical correlation is necessary to determine if elevated bilirubin is the result of non-GVHD-related liver toxicity. Do not report liver GVHD in this section.
Biopsy: a liver biopsy is a procedure in which a sample of liver tissue is taken percutaneously, transvenously, or laparoscopically.
Elevated hepatic venous pressure gradient: hepatic venous pressure gradient (HVPG) is a method used to detect portal hypertension. The procedure includes measuring the venous pressure before and after inflation of a fluid-filled balloon in the portal vein.
Elevated liver enzymes (e.g., alkaline phosphatase, ALT, AST, LDH, GGT): elevated liver enzymes may be a sign of liver toxicity, but clinical correlation is necessary to determine if elevated liver enzymes are the result of non-GVHD-related liver toxicity. Do not report GVHD in this section. Generally, elevated liver enzymes should be reported if they are two times the upper limit of normal at your center.
Hepatomegaly: hepatomegaly is the enlargement of the liver. Hepatomegaly is often detected upon physical examination, but may be detected using radiological techniques.
Right upper quadrant pain or tenderness: right upper quadrant (RUQ) pain or tenderness is often detected upon physical examination and is a general symptom that should be clinically correlated with other examinations for liver toxicity.
Ultrasonography / doppler (abnormal portal vein flow): Ultrasound can be used to determine if the flow through the hepatic portal vein is abnormal.
Weight gain > 5%: weight gain of greater than 5% is detected upon physical examination, but is a general symptom that should be clinically correlated with other assessment for liver toxicity.
Other: report other evaluations or signs/symptoms of liver toxicity in question 314.

Other Organ Impairment / Disorder

Question 315: 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 last report. If “yes,” continue with question 316. If “no,” continue with question 347.

Questions 316-346: Specify impairment/disorder and the date of diagnosis

Avascular necrosis: localized tissue death due to inadequate oxygen to the cells. Also known as coagulation necrosis or ischemic necrosis.
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%.
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 chemotherapy or radiation therapy and/or some viral infections (e.g., BK virus). Report cases with macroscopic (visible to the naked eye) or gross hematuria (WHO Grade III and IV hemorrhagic cystitis). If the etiology is infectious, also report in the Infection section (questions 231-235). 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.
Myocardial infarction (MI): an obstruction in the coronary artery resulting in damage/necrosis to the cardiac muscle.
Pancreatitis: inflammation of the pancreas.
Post-transplant thrombotic 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

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.

New Malignancy

Question 347: 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 6 Month to Two Year forms (revision 3, question 375-377).

If a new malignancy, lymphoproliferative disorder, or myeloproliferative disorder has occurred during this reporting period, check "yes" and continue with question 348. If not, check "no" and continue with question 390.

Question 348: 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 349. If "no," continue with question 351.

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 349: 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 350: 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 351-388: 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 applicable additional questions.

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

Question 389: 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.

Q390-394: Survival and Functional Status

Question 390: 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 the Subsequent HCT section at question 395.

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 the 14 days prior to the 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 391-392: 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 395. If "other" is selected, report the recipient's occupation in question 392.

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

Questions 393-394: 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 394.

Q395-402: Subsequent HCT

Complete this section if the recipient received a subsequent HCT (question 2, answered "yes"). If no subsequent HCTs were performed, continue with the DCI section at question 403.

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 398). 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 395: 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 396: Was the subsequent HCT performed at a different institution?

Indicate if the subsequent HCT was performed at another institution. If "yes," continue with question 397. If "no," continue with question 398.

Question 397: 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 398-399: 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 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 347 for more information). If the reason is a new malignancy, also complete questions 347-389.
- **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 399.

Multiple Products

In the FormsNet3^{SM} application, use the multiple feature to complete questions 400-402 for each product infused. For paper form submission, copy and complete questions 400-402 for each product infused.

Questions 400-402: 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 401 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 402 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 398).

Q403-501: Donor Cellular Infusion (DCI) Information

This section captures information on DCIs (question 4, answered “yes”) from any donor source (unstimulated peripheral blood mononuclear cells, T cells, NK cells, other cells) performed during the follow-up interval. Complete a 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 (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

The paper version of the Six Months to Two Years Post-HCT Data Form (2200) provides space to report one Donor Cellular Infusion (DCI) event (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. A DCI given for one of these reasons would be considered a subsequent HCT.

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 (PBSC, 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 (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.

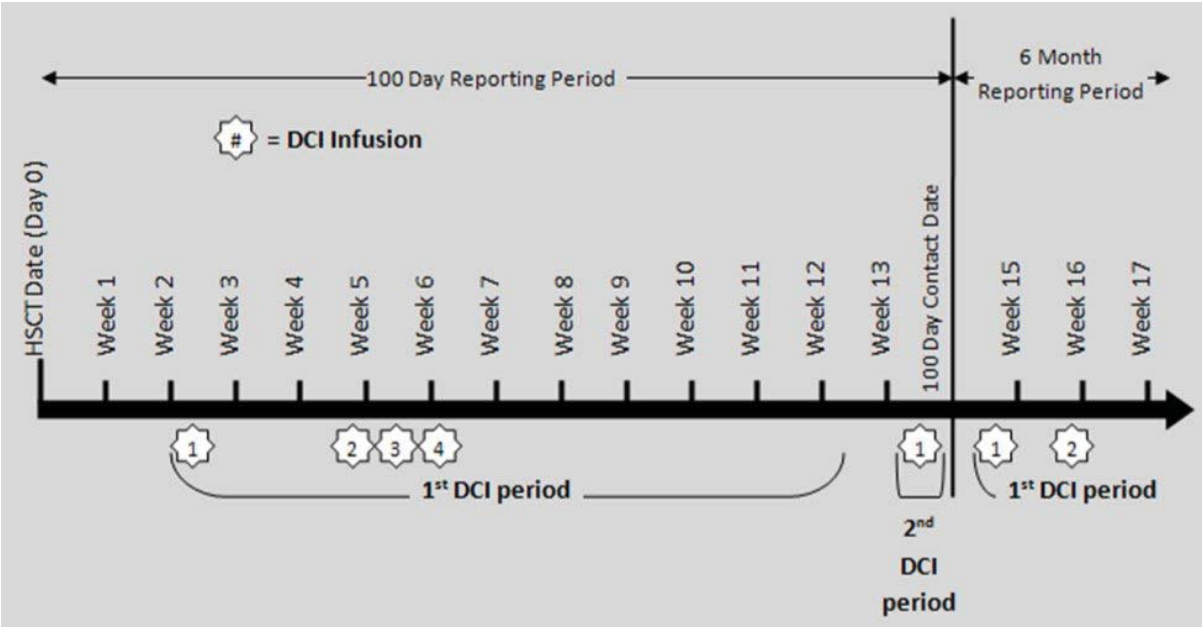
Complete the first DCI section for all infusions given between day 0 (of the DCI) and 10 weeks post initial DCI infusion. If the recipient receives an additional DCI, but it is infused after the initial 10-week period, report this subsequent DCI in a second DCI section. Any additional infusion(s) performed 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 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 403: Date the first DCI was given

Report the date of the 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 404: 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 the example above, the total number is four).

Question 405: Was the DCI infusion performed at a different institution?

Indicate if the DCI was performed at another institution. If “yes,” continue with question 406. If “no,” continue with question 407.

Question 406: 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 407: 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^{SM} 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 408-415.

- **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 416.
- **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. Lymphocytes may be infused to reduce and potentially eliminate host cells and improve donor cell percentage.

  If the reason is stable, mixed chimerism, also complete question 417. 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 infusion of donor T-cells is to restore 100% donor chimerism.

  If the reason is loss of/decreased donor T-cell chimerism, also complete question 417. 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 418.

Questions 408-413: 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 date the method was used prior to DCI date (question 403).

Questions 414-415: 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 415 and report the date of administration of the final chemotherapy dose. If “no,” continue with question 419.

Question 419: 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 421.

Question 420: 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 421: 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 422-428: 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 426.
- Isolated from a unit(s) of whole blood. If "yes," specify the number of units in question 428.

Question 429: 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 430. If "no," continue with question 433.

Question 430: 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 431: 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 432: Number of leukaphereses

Report the number of leukapheresis procedures.

Question 433: 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 PBSC used for allogeneic HCT. Indicate whether the donor received treatment to enhance cell collection prior to donation. If "yes," continue with question 434. If "no," continue with question 441.

Question 434-440: 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 438.
- **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 440.

Questions 441-447: 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 448: Were dendritic cells infused?

Indicate whether dendritic cells were infused.

Question 449: Were fibroblasts infused?

Indicate whether fibroblasts were infused.

Questions 450-451: Were any other cell types infused (not including cell types reported in questions 441-449)?

Indicate whether any other cell types were infused. If "yes," specify the cell type in question 451.

Question 452: Were the cells cryopreserved prior to infusion?

Indicate whether the cells were cryopreserved prior to infusion. If “yes,” continue with question 453. If “no,” continue with question 454.

Question 453: 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 454.

Question 454: 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 455. **Do not report cryopreservation as a method of manipulation**. If the product was not manipulated, check “no” and continue with the signature lines.

Question 455: 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 460) is performed for ABO or Rh incompatibility between the donor and recipient. Volume reduction as a manipulation method (question 467) 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 460 and 467, the product must be plasma reduced for ABO incompatibility and then further reduced to decrease the total product volume.

Question 456: 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 467. Indicate if the product was manipulated for ABO incompatibility. If "yes," continue with question 457. If "no," continue with question 464.

Questions 457-463: Specify method

Indicate the method(s) used for ABO incompatibility manipulation. If "other" is selected, specify the method in question 463.

Question 464: 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 465: 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 466: 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 467: 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 468: CD34+ selection

CD34+ selection is a manipulation method also known as “positive selection.” This method selects out 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 469. If “no,” continue with question 471.

Questions 469-470: Specify manufacturer of CD34+ selection machine

Indicate the type of machine used for CD34+ selection. If “other” is selected, specify the manufacturer in question 470.

Questions 471-481: 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 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 472-477, indicate the specific antibodies used for T-cell depletion in questions 484-501. If “other” is selected, specify the method in question 481.

CD34 Affinity Column Plus Sheep Red Blood Cell Rosetting (Question 479)
CD34 affinity column plus sheep red blood cell rosetting combines two methods (positive and negative selection) to achieve a greater degree of T-cell depletion. Sheep erythrocytes adhere spontaneously to human T cells forming rosettes. The rosettes are then isolated from the rest of the cells using Ficoll-Hypaque gradient centrifugation.

Questions 482-483: Other cell manipulation

Indicate if the cells were manipulated using any other method, and specify the manipulation type in question 483.

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 484: Were antibodies used during graft manipulation?

If antibodies were used during product manipulation, select “yes” and continue with question 485. If antibodies were not used, select “no” and continue with the signature lines.

Questions 485-501: 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 495. If “Anti CD52” is selected, further specify the antibody in questions 497-499. If “other antibody” is selected, specify in question 501.