2400: Pre-TED (Revision 4)

The Pre-TED Form is now required for all transplants, including subsequent transplants on the comprehensive report form track.

All transplant centers participating in the CIBMTR must submit a Pre-TED Form for each allogeneic (related or unrelated) hematopoietic cell transplant (HCT). The Pre-TED is a requirement of the SCTOD for all United States transplant centers when either the stem cell donation or the transplant occurs within the United States. For more information regarding the SCTOD, see General Instructions, Stem Cell Therapeutics Outcomes Database.

Centers are required to complete a Pre-TED Form (F2400) for all autologous transplant recipients, whether or not they agree to have their data used in research.

The Pre-TED may be submitted to the CIBMTR without the consent of the recipient because the CIBMTR meets the definition of a Public Health Authority (PHA) under the Health Insurance Portability and Accountability Act (HIPAA). In this capacity the CIBMTR is authorized to collect individually identifiable health information without consent or authorization of the individual. The PHA designation also allows transplant centers, which fit the definition of covered entities, to disclose these data to CIBMTR under 45 CRF 164.512 (Privacy Rule) without the direct consent or authorization of the recipient.

For autologous transplant recipients who do not provide consent for the CIBMTR research database, completion of forms other than the Pre-TED will not be required. Data collected on the Pre-TED forms will not be used in research. Important factors supporting this change include:

- These data are essential to maintain the epidemiological integrity of the outcomes registry by allowing us to confirm that transplant recipients reported in research studies are representative of all recipients transplanted.
- Pre-TED data will make federally required annual Center Volumes report more complete and better able to inform the public about the types of HCTs occurring in the United States.

The Pre-TED may be submitted to the CIBMTR up to two weeks prior to the start of the recipient's preparative regimen (see Helpful Hint below). The Pre-TED is due the day of the HCT (day 0), and is past due if not received by that date.

Helpful Hint:
In order to avoid having to make changes to the HCT date, complete the data for the Pre-TED (in FormsNet3SM or on paper), but do not submit the form until the first dose of the preparative regimen is given.

For recipients receiving a subsequent HCT:
Transplant centers must submit a Pre-TED for all subsequent HCTs; this includes recipients assigned to the TED Forms and the Comprehensive Report Forms by the form selection algorithm.

For the majority of subsequent HCTs, the recipient will remain on the original follow-up form track assigned by the form selection algorithm. For more information regarding center type and the form selection algorithm, see General Instructions, Center Type and Data Collection Forms. A recipient may need to change tracks if enrolled on a study that requires comprehensive forms.

For recipients of multiple transplants, transplant centers are not granted access to the new Pre-TED Form in FormsNet3SM until the Post-TED or Form 2100/2200/2300 from the previous transplant has been completed.

Transplant centers can use the FormsNet3SM 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.

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
6/ 24/ 16	2400: Pre-TED	Add	Added information box to Q568: "Never Treated" is not an option choice on revision four of the Pre-TED Form. When completing revision four of this form, centers should report "No Response (NR) / Stable Disease (SD)" for recipients who have only received supportive care prior to transplant.
4/6/ 16	2400: Pre-TED	Modify	Updated donor section reflect reporting of different products from same donor in questions 46-50: ~~Previous CIBMTR forms required you to enter two instances of the donor section when a single donor donated multiple products. This is no longer required. Report all products collected from a single donor in the same instance of the donor section.~~ If the recipient receives a cord blood unit and another product from the same related donor, complete two instances of the Donor Information section (questions 31-62) on the Pre-TED Form 2400. For example, if a related donor gave a cord blood unit and bone marrow, you would report the cord blood unit information in one instance with the donor type listed as 'Related cord blood unit'. Create another instance with the donor type reported as 'Related donor' to report the bone marrow information. This allows CIBMTR to capture all the necessary donor information needed. For these cases, complete a Form 2004 for each product. When the donor type is an HLA matched or mismatched relative, only one Form 2005 is required.
3/ 31/ 16	2400: Pre-TED	Add	Added an information box about transformation of polycythemia vera and essential thrombocythemia to question 525: Myelofibrosis that develops in patients with essential thrombocythemia (ET) or polycythemia vera (PV) is considered secondary myelofibrosis. Do not report this as a transformation; when a patient with ET or PV develops fibrosis, do not report primary myelofibrosis as the primary indication for transplant.
3/ 31/ 16	2400: Pre-TED	Modify	Changed disease characteristics for plasma cell leukemia in question 589 to: ~~more than~~ ≥ 20% plasma cells in the peripheral differential white blood cell count
3/ 31/ 16	2400: Pre-TED	Modify	Added table explaining how to report IgG versus IgM CMV results to question 93. [see table in text]
2/9/ 16	2400: Pre-TED	Modify	Modified text in obesity comorbidity to include pediatric patients: **Obesity:** Patients with a body mass index > 35 kg/m^2 or *BMI-for-age ≥ 95% (pediatric recipients only) during pre-transplant work-up period.*
2/9/ 16	2400: Pre-TED	Modify	Changed the text of question 53 to: Report the total number of mobilization events performed *for this HCT*. Include all mobilization events, *even if a product from the mobilization event for this HCT was*

			not used during the transplant. For example, if 2 mobilization events were performed to collect enough stem cells for this transplant, but the first collection wasn't necessary for the transplant, report two mobilization events.
12/ 9/15	2400: Pre-TED	Modify	Edited the following text in question 62: Stem cells do not typically circulate in the bloodstream. 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*. Indicate if the donor received plerixafor at any time prior to the ~~preparative regimen.~~ *start of stem cell collection.*
12/ 7/15	2400: Pre-TED	Modify	Added MPN to the following text in the MDS/MPN Disease specific section: If the recipient is being transplanted for AML that has transformed from MDS/ *MPN* , the primary disease for HCT must be reported as AML. Disease Classification questions must be completed for both AML and MDS/ *MPN* .
12/ 3/15	2400: Pre-TED	Modify	Updated question 420 to refer to all tyrosine kinase inhibitors: *There is currently an issue on this form. Question 420 should say "e.g. imatinib mesylate." Report any tyrosine kinase inhibitors, rather than just imatinib mesylate.* Report if the recipient *received any tyrosine kinase inhibitors (TKI). Examples of TKIs include Imatinib mesylate (Gleevec, Glivec, STI-571, or CGP57148B), dasitinib (Sprycel), and nilotonib.* Indicate "yes" or "no."
12/ 3/15	2400: Pre-TED	Add	Added the following text to question 158: Based on the CIBMTR operational guidelines below, report if the regimen was myeloablative, reduced intensity, or non-myeloablative. The determination of whether the intent of the regimen was reduced intensity or non-myeloablative should be based either on the protocol at your center or the opinion of the physician overseeing the care of the recipient at your center. *However, if there's a protocol utilized at your center that doesn't fall within CIBMTR operational guidelines for regimen intensity, you may report the regimen intensity based on the protocol intent.*
12/ 3/15	2400: Pre-TED	Add	Added the following text to questions 366-401: If question 365 indicates that abnormalities were identified, each of questions 366-400 must be answered as "yes" or "no." Do not leave any response blank. Indicate "yes" for each cytogenetic abnormality identified at any time prior to the start of the preparative regimen. Indicate "no" for all options not identified by cytogenetic assessment at any time prior to the start of the preparative regimen. *For cases where AML has transformed from MDS, only report "yes" for cytogenetic abnormalities identified on or after the date of diagnosis for AML.* If one or more abnormalities are best classified as "other abnormality," specify in question 401.
9/ 27/ 15	2400: Pre-TED	Modify	Modified MDS transformation table to include RA, 5q- syndrome, MDS-U, and chronic eosinophilia transformations
9/ 27/ 15	2400: Pre-TED	Modify	Modified myeloablative, reduced intensity, and non-myeloablative regimens table for **thiopeta.** Thiotepa ≥ (greater than or equal to) 10 mg/kg is myeloablative, and thiotepa < (less than) 10 mg/kg is non-myeloablative.

6/26/15	2400: Pre-TED	Modify	Modified text in question 525: Indicate if the recipient's disease progressed to AML or transformed into a different MDS/MPN subtype between initial diagnosis and the start of the preparative regimen. Approximately one third of MDS cases transform into AML, signifying a poorer prognosis. Progression to AML is defined by an increase in **blood or** bone marrow blasts equal to or greater than 20%.
6/12/15	2400: Pre-TED	Modify	Modified the informational text in question 168 and before question 316: ~~ATG or alemtuzumab (Campath) given for GVHD prophylaxis planned prior to Day 0 should be reported in the preparative regimen section of the Pre-TED. If ATG, alemtuzumab, or cyclophosphamide is planned after Day 0, it should be reported in the GVHD prophylaxis section (questions 316-341).~~ For ATG, Campath, and Cyclophosphamide: If these agents are given for GVHD prophylaxis both prior to and after Day 0, they must be reported in separate sections of the Pre-TED form. Report doses given prior to Day 0 in the preparative regimen section of the Pre-TED (questions 168-315). If given after Day 0 as GVHD prophylaxis, report in the GVHD prophylaxis section of the Pre-TED (questions 316-341).
6/5/15	2400: Pre-TED	Remove	Removed the following words from the comorbidities section in question 97: Hepatic (mild): Chronic hepatitis, bilirubin > upper limit of normal to 1.5x upper limit of normal, or AST/ALT > upper limit of normal to 2.5x upper limit of normal ~~at the time of transplant~~, or any history of hepatitis B or hepatitis C infection. *See note in question 96.*
6/5/15	2400: Pre-TED	Add	Added the following warning box to question 6: There is an exception to this guidance. **Do not report a 10-CBA recipient's participation using this question**; select "no" for question 6 if the patient is enrolled in 10-CBA.
6/5/15	2400: Pre-TED	Modify	Modified the explanation for question 451: ~~If more than one "other molecular marker" is identified, add an additional instance in the FormsNet application for questions 453-454.~~ … Assessments for other molecular markers known or believed to be associated with ALLmay be performed. If these studies are performed, indicate ~~"yes"~~ **"positive" or "negative"** and specify **the marker** in question 454. **If another molecular marker was not performed, select "not done."**
6/5/15	2400: Pre-TED	Modify	Modified the explanation for question 403: ~~Add an additional instance in the FormsNet application for questions 410-411 if more than one "other molecular marker" is identified.~~ … Assessments for other molecular markers known or believed to be associated with AML may be performed. If these studies are performed, indicate ~~"yes"~~ **"positive" or "negative"** and specify **the marker** in question 411. **If another molecular marker was not performed, select "not done."**
5/29/15	2400: Pre-TED	Modify	Modified to the explanatory text for question 619: If the recipient had amyloidosis **or POEMS syndrome,** but no evidence of myeloma, select "not applicable" and continue with the signature line.
5/16/15	2400: Pre-TED	Modify	Removed the following text from the main page: ~~Although data regarding recipients receiving autologous HCT are not required to be submitted as part of the C.W. Bill Young Transplant Program, the CIBMTR is highly committed to collecting data on these recipients for research studies.~~

			~~Centers choosing to report autologous data to the CIBMTR must report on all autologous transplants performed at their center. For more information regarding data reporting for autologous HCT, see General Instructions, Autologous Hematopoietic Stem Cell Transplant.~~ and added information about autologous reporting: "Centers are required to complete a Pre-TED Form (F2400) for all autologous transplant recipients, whether or not they agree to have their data used in research. … • Pre-TED data will make federally required annual Center Volumes report more complete and better able to inform the public about the types of HCTs occurring in the United States."
5/16/15	2400: Pre-TED	Modify	Removed the following text from Q159: ~~Use the earliest date from questions 161-167 (radiation) or questions 168-315 (chemotherapy). All dates reported in the preparative regimen section must be equal to or after the date reported for this question.~~ and added information about autologous reporting: "Use the earliest date from questions 163, (radiation), or 170-236, 253-311 (systemic therapy) and 314. Additional radiation and/or intrathecal chemotherapy start dates may be prior to the date the preparative regimen began."

Q1-10: Recipient Data

Question 1: Date of Birth

The date of birth is automatically populated based on the value reported on the CRID Assignment Form (2804). Verify that the date of birth is correct. If an error is noted, correct Form 2804 and verify that the date of birth has been updated on the Pre-TED Form.

Question 2: Sex

The recipient's sex is automatically populated based on the value reported on the CRID Assignment Form (2804). Verify that the recipient's sex is correct. If an error is noted, correct Form 2804 and verify that the recipient's sex has been updated on the Pre-TED Form.

Question 3: Ethnicity

Indicate the recipient's ethnicity. The United States Office of Management and Budget (OMB) has defined ethnicity as culturally or geographically determined. The distinction between Hispanic and non-Hispanic is for the purpose of the United States census and reporting of SCTOD data. According to the OMB, "Hispanic" is an ethnic designation based upon where someone (his or her ancestors) was raised (e.g., "Latin America"). Hispanic people may be of any race. The CIBMTR recognizes regional differences with regard to the interpretation of ethnicity throughout the world.

If the recipient is not a resident of the USA, select "not applicable."

If the recipient declines to provide this information or the recipient's ethnicity is not documented, select "unknown."

For more information regarding ethnicity, see Appendix I.

Question 4, Reporting More Than One Race

FormsNet3℠ application: Complete question 4 for each race the recipient identifies with by adding an additional instance in the FormsNet application.
Paper form submission: Copy question 4 and complete for each race the recipient identifies with.

Question 4: Race

Indicate the recipient's race. If this recipient has reported that they are more than one race, you may indicate each race by adding an additional instance in the FormsNet application. The race groups provided are specific to the United States.

For non-U.S. centers, select "not reported" if the rules/regulations of your country prohibit the collection or reporting of race data (or due to lack of documentation). If race is reported, it may be necessary to consult with the recipient to select the race group(s) with which they most closely identify.

If the recipient declines to provide this information, select "not reported."

If the recipient's race is not documented, select "unknown."

For more information regarding race, see Appendix I.

Question 5: ZIP or postal code for place of recipient's residence (USA recipients only)

Enter the ZIP code in which the recipient resides.

Question 6: Is the recipient participating in a clinical trial?

Indicate if the recipient is a registered participant with BMT-CTN, RCI-BMT, USIDNET, COG, and/or another clinical trial sponsor that uses CIBMTR forms to capture outcomes data. If "yes," continue with question 7. If "no," continue with question 11.If the participant is enrolled in multiple studies, even if from the same sponsor, report each study separately.

- BMT-CTN: Blood and Marrow Transplant Clinical Trials Network
- RCI-BMT: Resource for Clinical Investigation in Blood and Marrow Transplant
- USIDNET: United States Immunodeficiency Network
- COG: Children's Oncology Group

! There is an exception to this guidance. **Do not report a 10-CBA recipient's participation using this question**; select "no" for question 6 if the patient is enrolled in 10-CBA.

Questions 7-10 Reporting Participation in More Than One Study

FormsNet3^{SM} application: Complete questions 7-10 for each study the recipient is participating in by adding an additional instance in the FormsNet application.

Paper form submission: Copy questions 7-10 and complete for each study in which the recipient is participating.

Questions 7-8: Study Sponsor

Select the study sponsor of the clinical trial the recipient is participating in. If the participant is enrolled in multiple studies, even if from the same sponsor, report each study separately.

If the study sponsor is reported as “BMT-CTN” or “RCI-BMT,” continue with question 9.

If the study sponsor is reported as “USIDNET” or “COG,” continue with question 10.

If “other sponsor” is reported, specify the study sponsor in question 8 and continue with question 10.

Question 9: Study ID Number

Select the recipient’s Study ID number.

Question 10: Subject ID

Enter the recipient’s USIDNET, COG, or other sponsor Subject ID.

If the recipient is participating in a BMT-CTN study and the EMMES ID is known, enter it here.

If the recipient is participating in an RCI-BMT study, enter the Subject ID given at the time of successful enrollment.

Q11-28: Hematopoietic Cellular Transplant (HCT)

Question 11: Date of this HCT

Report the intended start date of the HCT. If the infusion is planned to last several days, enter the **first** day the infusion is scheduled to start.

If the Pre-TED was submitted prior to day 0, and the planned infusion date has changed, the original planned date of the HCT will automatically be reported in FormsNet3SM on either the Post-TED or the 100 Days Post-HCT Data Form (Form 2100). For the recipient's first transplant, the HCT date may be changed on the Form 2814. For a subsequent transplant, the date may be changed on the form (Form 2100/2200/2300 or 2450) where the subsequent transplant was originally reported.

If the recipient is scheduled to receive a combination of cellular therapy and stem cell infusions, contact your center's CIBMTR CRC for reporting requirements.

Question 12: Was this the first HCT for this recipient?

Indicate if this is the recipient's first transplant. First transplant is defined as the first transplant the recipient ever receives, not the first transplant the recipient receives at your facility.

If "yes," and this is an autologous transplant, continue with question 13.

If "yes," and this is an allogeneic transplant, continue with question 29.

If "no," continue with question 15.

Question 13: For autologous HCTs only: Is a subsequent HCT planned as part of the overall treatment protocol (not as a reaction to post-HCT disease assessment)?

If, at the time of the current HCT, a second (tandem transplant) or subsequent HCT is planned according to the protocol, check "yes" even if the recipient does not receive the planned subsequent HCT. The word "planned" **should not** be interpreted as: *if the recipient relapses, then the "plan" is to perform a subsequent HCT.* If "yes," continue with question 14. If "no," continue with question 29.

Question 14: Specify subsequent HCT planned:

Indicate whether the planned subsequent HCT is autologous or allogeneic and continue with question 29.

Question 15: Specify the number of prior HCTs:

Enter the number of prior HCTs for the recipient. An HCT event is defined as an infusion of mobilized peripheral blood stem cells (PBSC), bone marrow, or cord blood. For more information on how to distinguish infusion types [example: HCT versus donor cellular infusion (DCI)], see Appendix O.

For recipients who have received a previous HCT (prior to the HCT for which this form is being completed), the following are examples of how to calculate the number of prior HCTs.

Example 1: A recipient was previously transplanted under a protocol that included an infusion of cells over multiple days: day 0, day +1 and day +2. This series of infusions is considered one HCT event (as opposed to three HCT events) and should be counted as *HCT Event #1*.
After receiving the infusion, the recipient had relapse of disease. The recipient is scheduled to receive a subsequent HCT including a preparative regimen. This HCT is *HCT Event #2.* One prior HCT should be reported.

Example 2: A recipient previously received an **allogeneic** HCT (*HCT Event #1*). Then, due to delayed neutrophil recovery, the recipient received additional cryopreserved **allogeneic** mobilized PBSC from the original donor, without a preparative regimen (i.e., "boost" – *HCT Event #2*).
After receiving the boost, the recipient had relapse of disease. The recipient is scheduled to receive a subsequent allogeneic HCT with preparative regimen (*HCT Event #3*). Two prior HCTs should be reported.

Example 3: A recipient previously received an **autologous** HCT (*HCT Event #1*). Then due to delayed neutrophil recovery, the recipient received additional cryopreserved **autologous** cells without a preparative regimen (i.e., "boost" which is not counted as an HCT event because the intent of the autologous infusion is to treat the graft failure).
The boost is successful, but a few years later the recipient develops a new malignancy. The recipient is scheduled to receive a subsequent autologous HCT with preparative regimen (*HCT Event #2*). One prior HCT should be reported.

> ! **If the recipient receives an infusion due to poor graft response, count the infusion as a subsequent HCT.** The exception to this is "autologous rescue." Autologous rescue **should not be** counted as a separate HCT, and the data collection forms **will not** start over (i.e., the forms will continue from the previous HCT).

Questions 16-19: What was (were) the prior HCT source(s)?

Select the cellular source for each of the recipient's previous HCTs as either autologous, allogeneic unrelated, allogeneic related, or syngeneic (identical twin).

Question 20: Date of the last HCT (just before current HCT):

Report the date of the recipient's last autologous or allogeneic (related or unrelated) HCT. Although the CIBMTR requests a Pre-TED for each HCT, there may be circumstances where a prior HCT was not reported (e.g., prior autologous HCT or HCT performed at another center). Reporting the recipient's last HCT enables the CIBMTR to appropriately account for recipient survival status in the database.

Question 21: Was the last HCT performed at a different institution?

Indicate if the last HCT was performed at another institution. If "yes" continue with question 22. If "no" continue with question 23.

Question 22: Specify the institution that performed the last HCT:

Report the name, city, state, and country of the institution where the recipient's last HCT was performed. These data are used to identify and link the recipient's existence in the database and, if necessary, obtain data from the previous transplant center.

Question 23: What was the HSC source for the last HCT?

Report the stem cell source of the recipient's last HCT as either autologous, allogeneic unrelated or allogeneic related (including syngeneic).

Question 24-28: Reason for current HCT:

Indicate the reason for the current HCT (check only one). If this was a subsequent transplant, verify that this answer is consistent with the reason for the subsequent transplant reported on the previous series of report forms.

- **No hematopoietic recovery:** Additional stem cells are required because the recipient did not recover their granulocytes following previous high-dose therapy and HCT.

- **Partial hematopoietic recovery:** Additional stem cells are required because the recipient's hematopoietic recovery was deemed insufficient or too slow for the recipient to survive following previous high-dose therapy and HCT (ANC was never greater than or equal to 0.5×10^9/L for three consecutive days).

- **Graft failure/rejection after achieving initial hematopoietic recovery:** Additional stem cells are required because the recipient's hematopoietic recovery declined indefinitely after the initial hematopoietic recovery (ANC was greater than or equal to 0.5×10^9/L for three consecutive days, and

then declined to below 0.5 × 10^9/L for three consecutive days). If the reason is graft failure or rejection after initial recovery, also complete question 25.

- **Persistent primary disease:** Additional stem cells are required because the recipient was transplanted with disease present, and never entered a remission following the previous transplant.

- **Recurrent primary disease:** Additional stem cells are required because the disease for which the recipient was transplanted relapsed following the previous transplant. If the reason is recurrent primary disease, also complete question 26. Ensure that the date of recurrent primary disease matches the relapse/progression date reported on the previous transplant's appropriate follow-up form.

- **Planned second HCT, per protocol:** Additional stem cells are given because the protocol planned for a subsequent transplant/infusion. This includes *all planned* subsequent transplants (including triple or quadruple transplants). 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. If the reason is a new malignancy, also complete question 27, and attach a copy of the pathology report using the Log of Appended Documents (Form 2800). Ensure that the date of diagnosis for the new malignancy matches the date of diagnosis for the new malignancy reported on the previous transplant's appropriate follow-up form.

- **Stable, mixed chimerism:** 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:** Additional stem cells are required because the percentage of donor cells present versus recipient cells present is decreasing. This is usually due to an underlying cause such as graft failure, graft rejection, or recurrent disease.

- **Other:** Additional stem cells are required and/or given for a reason other than the options listed. If the HCT is for another reason, select "other" and complete question 28.

Q29-62: Donor Information

Question 29: Multiple donors

Indicate if cells from multiple different donors (multiple CBUs, combinations of other products from different donors) are to be used for this HCT. If “yes,” continue with question 30. If “no,” continue with question 31.

A supplemental infusion is defined as an infusion of cells given prior to clinical day 0 (of an HCT) for any reason other than to produce engraftment. An infusion of supplemental cells is often given in conjunction with a preparative regimen for HCT. Supplemental infusions should be included when determining if multiple donors were used for this HCT event.

For more information on supplemental infusions, see Appendix O.

Question 30: Specify number of donors

Report the number of donors used for this HCT. Note that this value should never be “1,” since multiple donors were reported in question 29.

Related CBU and Related Product from Same Donor
If the recipient receives a cord blood unit and another product from the same related donor, complete two instances of the Donor Information section (questions 31-62) on the Pre-TED Form 2400.For example, if a related donor gave a cord blood unit and bone marrow, you would report the cord blood unit information in one instance with the donor type listed as ‘Related cord blood unit’. Create another instance with the donor type reported as ‘Related donor’ to report the bone marrow information. This allows CIBMTR to capture all the necessary donor information needed. For these cases, complete a Form 2004 for each product. When the donor type is an HLA matched or mismatched relative, only one Form 2005 is required.

Question 31: Specify donor

Reporting More Than One Donor
FormsNet3^{SM} application: Complete questions 31-62 for each donor by adding an additional instance in the FormsNet application.
Paper form submission: Copy questions 31-62 and complete for each donor.

Indicate the donor type for this product.

An **autologous** product has cells collected from the recipient for his/her own use.

> If the product was autologous (marrow, PBSC, other product), select “autologous” and continue with question 46.
>
> If the product was an autologous cord blood unit, select “autologous cord blood unit” and continue with question 35.

An **unrelated donor (allogeneic, unrelated)** is a donor who shares no known ancestry with the recipient. Include adoptive parents/children or stepparents/children. Distinguish if the product in an NMDP product or a non-NMDP product. Examples of non-NMDP donor registries include, but are not limited to: St. Louis Cord Blood Bank, Anthony Nolan, and StemCyte International Cord Blood Center.

> If the product was an NMDP unrelated cord blood unit, select “NMDP unrelated cord blood unit” and continue with question 32.
>
> If the product was from an NMDP unrelated donor (marrow, PBSC, other product), select “NMDP unrelated donor” and continue with question 33.
>
> If the product was from a non-NMDP unrelated donor and was facilitated through another registry, select “non-NMDP unrelated donor” and continue with question 34.
>
> If the product was a non-NMDP cord blood unit, select “non-NMDP cord blood unit” and continue with question 35.

A **related donor (allogeneic or syngeneic, related)** is a blood-related relative. This includes monozygotic (identical twins), non-monozygotic (dizygotic, fraternal, non-identical) twins, siblings, parents, aunts, uncles, children, cousins, half-siblings, etc.

> If the product was from a related donor (marrow, PBSC, other product), select “related donor” and continue with question 40.
>
> If the product was a related cord blood unit, select “related cord blood unit” and continue with question 35.

Question 32: NMDP cord blood unit ID

Report the NMDP Cord Blood Unit ID. This information is included on the product label, the paperwork accompanying the product, and within the NMDP search/product documentation. The ID is always numeric and begins with “9” (e.g., 9000-0000-0). If the product ID does not begin with a “9,” the product may not be

an NMDP cord blood unit and the source of the product should be double-checked. Enter the NMDP cord blood unit ID and continue with question 46.

Question 33: NMDP donor ID

Report the NMDP Donor ID (e.g., 0000-0000-0). This ID is unique for each donor and is assigned by NMDP. This information is included on the product label, the paperwork accompanying the product, and within the NMDP search/product documentation. Enter the NMDP Donor ID (e.g., 0000-0000-0) and continue with question 46.

Question 34: Non-NMDP unrelated donor ID (not applicable for related donors)

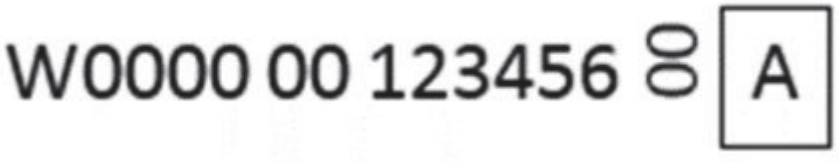
Report the non-NMDP unrelated donor ID. Examples of non-NMDP donor registries include, but are not limited to: Anthony Nolan, Australia Bone Marrow Donor Registry, and REDOME. This ID is often located on the product label, the paperwork accompanying the product, and registry-specific search/product documentation. Enter the non-NMDP unrelated donor ID and continue with question 38.

Question 35: Non-NMDP cord blood unit ID (include related and autologous CBUs)

Report the non-NMDP cord blood unit ID. Examples of non-NMDP donor registries include, but are not limited to: St. Louis Cord Blood Bank and StemCyte International Cord Blood Center. This ID is often located on the product label, the paperwork accompanying the product, and registry-specific search/product documentation. Enter the non-NMDP cord blood ID. Note that some cord blood banks can ship their units either through the NMDP or directly to the transplant center. Carefully review the accompanying documentation to determine which is appropriate for your unit. You may wish to consult with your center's Transplant Coordinator, as he or she will have insight as to how the product was acquired.

Question 36: Is the CBU ID also the ISBT DIN number?

Report "yes" if the non-NMDP CBU ID is the same as the International Society of Blood Transfusion (ISBT) Donation Identification Number (DIN) and continue with question 38. If the product has an ISBT label on it, the ISBT DIN number is in the upper-left-hand corner and consists of a letter followed by 12 numbers, two sideways numbers, and a letter in a box. Example below:



Please find additional information regarding the ISBT DIN numbers and traceability at http://www.iccbba.org/docs/public/introduction_traceability.pdf. For example, you may see a barcode with an alphanumeric string below it.

If the CBU ID is not the same as the ISBT DIN number, select “no” and continue with question 37.

Question 37: Specify the ISBT DIN number:

Report the ISBT DIN number using the letter, 12 digits, 2 sideways numbers, and the letter in the box.

Questions 38: Registry or UCB Bank ID:

FormsNet3^{SM} application: Select the appropriate registry code from the drop down directory.
Paper form submission: Use the BMDW website to look up the registry’s appropriate match code. **Enter the match code listed in brackets.** http://www.bmdw.org/index.php?id=addresses_members&no_cache=1
Example: Registry Name: Against Leukemia Foundation Marrow Donor Registry
Match codes: Poland-ALF [PL3]
Report on the Pre-TED: PL3

Specify the registry used to obtain the adult donor or umbilical cord blood unit. The Bone Marrow Donors Worldwide (BMDW) codes have been adopted to avoid submitting the entire name and address of the donor registry.

The registry code for NMDP donors is USA1 and for NMDP cord units is U1CB.

Some common banks that do not list with BMDW have been added to the FormsNet list for version 4, including St Louis Cord Blood Bank (SLCBB) and Viacord (VIAC).

If the donor was found through DKMS, report the registry that facilitated the HCT. Some registries may be listed more than once with BMDW (one way for marrow/PBSC products and differently for cord blood products). Ensure that the appropriate code for the product was selected because distribution of data depends on the code.

If the registry code cannot be determined using the BMDW website, select “other registry” and continue to question 39.

Question 39: Specify other Registry or UCB Bank

If the BMDW website does not list a match code for the adult donor registry or cord blood bank, provide the registry's official name in the "specify other registry" field.

Please ensure that the registry you are entering under "other" is not already listed in the pull-down list for question 38. For example, NMDP adult donors, NMDP cords, and New York Cord Bank each have their own entries above in the registry or UCB Bank ID drop down menu.

Question 40: Specify the related donor type:

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

Syngeneic:
Includes: Monozygotic (identical) twins. Occurs when a single egg is fertilized to form one zygote, which then divides into two separate embryos.
Does not include: Other types of twins or HLA-identical siblings (see below).

HLA-identical sibling:
Includes: Non-monozygotic (dizygotic, fraternal, non-identical) twins. Occurs when two eggs are fertilized by two different sperm cells at the same time. This category also includes siblings who aren't twins, but have identical HLA types.
Does not include: Half-siblings (report as "HLA matched other relatives" if their HLA is a match, or "mismatched relative" if it does not match).

HLA-matched other relative:
Includes: All blood-related relatives, other than siblings, who are HLA matched (e.g., parents, aunts, uncles, children, cousins, half-siblings).
Does not include: Adoptive parents/children or stepparents/children who are HLA matched.

HLA-mismatched relative:
Includes: Siblings who are not HLA-identical and all other blood-related relatives who have at least one HLA mismatch (e.g., parents, aunts, uncles, children, cousins, half-siblings).
Does not include: Adoptive parents/children or stepparents/children

Questions 41-42: Date of birth: (donor/infant)

Report if the donor's/infant's date of birth is "known" or "unknown." If the donor's/infant's date of birth is "known," report the date of birth (YYYY-MM-DD) and continue with question 45. If the donor's/infant's date of birth is "unknown," continue with question 43.

Questions 43-44: Age: (donor/infant)

Report if the donor's/infant's age is "known" or "unknown." If the donor's/infant's age is known, report the donor's/infant's age at the time of product collection in question 44. Report the age in months if the donor is less than 1 year old, otherwise report the age in years. If the donor's/infant's age at collection is unknown, continue with question 45.

Question 45: Sex: (donor/infant)

Indicate the donor's biological sex as "male" or "female." For cord blood units, report the infant's sex.

Questions 46-50: Specify product type:

Indicate "yes" or "no" for each product type listed for the donor specified in question 31.

If the recipient receives a cord blood unit and another product from the same related donor, complete two instances of the Donor Information section (questions 31-62) on the Pre-TED Form 2400.

For example, if a related donor gave a cord blood unit and bone marrow, you would report the cord blood unit information in one instance with the donor type listed as 'Related cord blood unit'. Create another instance with the donor type reported as 'Related donor' to report the bone marrow information. This allows CIBMTR to capture all the necessary donor information needed.

For these cases, complete a Form 2004 for each product. When the donor type is an HLA matched or mismatched relative, only one Form 2005 is required.

Examples of "other product" type include, but are not limited to the following:

- Supplemental infusion of NK Cells
- Supplemental infusion of T-regulatory cells
- Supplemental infusion of mesenchymal cells

If "other product" is indicated, report the product type in "specify other product type." If your center has a protocol where using "other products" is common, you should be consistently reporting the same text in the specify field so that the like products can be grouped together.

Question 51: Specify number of products infused from this donor:

Report the number of products infused from the donor specified in question 31.

Single Product: CIBMTR defines a *single product* (i.e., cellular product) as **cells collected from a single donor using the same mobilization cycle and collection method regardless of the number of collection days.**

Example 1 (multiple bags): A G-CSF-stimulated donor had two PBSC collections on subsequent days. The products collected over the two days were divided into four bags. Although the product is contained in multiple bags, this collection is considered a single product, as there was no change in mobilization technique or collection method.

Multiple Products: For the purposes of this manual, the CIBMTR defines *multiple products* as **cells collected using more than one mobilization technique and/or collection method.**

Example 2 (multiple collection methods): A G-CSF-stimulated donor had a PBSC collection and the product was cryopreserved. One month later the donor had a marrow collection; both products were infused at the time of transplant. Each collection is considered a separate product because different collection methods were used.

Example 3 (change in mobilization): A G-CSF-stimulated donor had a PBSC collection, but the cell count was poor. GM-CSF was administered and the donor was re-collected. Each collection is considered a separate product due to the change in mobilization.

Example 4 (re-mobilization): A G-CSF-stimulated donor had a PBSC collection, but the cell count was poor. The donor was re-mobilized with G-CSF and a second PBSC collection was performed. Each collection is considered a separate product due to the re-mobilization of the donor.

Example 5 (two different product types): A cord blood unit is infused at the same time as marrow. Each collection is considered a separate product.

! The following mobilization questions are for autologous HCT recipients only. If other than autologous, continue with question 60.

Question 52: Did the recipient have more than one mobilization event to acquire cells for HCT?

Stem cells do not typically circulate in the bloodstream. Therefore, in order to increase the quantity of cells for collection, an agent is frequently given to the 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*. Occasionally, a bone marrow product may be primed using a growth factor.

For the purposes of this manual, the CIBMTR defines a *mobilization event* as the planned administration of growth factors or systemic therapy designed to enhance stem cell collection. If the donor requires an additional mobilization at a later date to collect an additional product, this should be considered an additional mobilization event. Additionally, if the mobilization methods change (e.g., plerixafor is required starting on Day 3 of collection) this would be considered an additional mobilization event.

Example 1: An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection. Since the collection and mobilization methods remained the same over the duration of the collection, this is considered one mobilization event.

Example 2: An autologous recipient was mobilized with G-CSF and underwent a two-day PBSC collection, but the cell count was poor. GM-CSF was administered and the autologous recipient was re-collected. This is considered two mobilization events due to the change in mobilization.

Example 3: An autologous recipient was mobilized with G-CSF and underwent a one-day PBSC collection, but the cell count was poor. The recipient then received plerixafor to enhance the mobilization. This is considered two mobilization events due to the change in mobilization.

Question 53: Specify the total number of mobilization events performed for this HCT (regardless of number of collections or which collections were used for this HCT):

Report the total number of mobilization events performed for this HCT. Include all mobilization events, even if a product from the mobilization event for this HCT was not used during the transplant. For example, if 2 mobilization events were performed to collect enough stem cells for this transplant, but the first collection wasn't necessary for the transplant, report two mobilization events.

Questions 54-59: Specify all agents used in the mobilization reported above:

Report if any of the following products were used in the mobilization event(s) reported in questions 52-53. Select "yes" or "no" for each question.

G-CSF: granulocyte colony-stimulating factor, filgrastim, Neupogen®
GM-CSF: granulocyte macrophage colony-stimulating factor, sargramostim, Leukine®
Peglygated G-CSF: pegfilgrastim, Neulasta®
Plerixafor: Mozobil®
Other CXCR4 inhibitor: examples include POL6326 and AMD3465. Report experimental and other CXCR4 inhibitors used to mobilize the donor here.
Combined with chemotherapy: Systemic therapies used to enhance the stem cell product may include cyclophosphamide or ICE chemotherapy (Ifosfamide, carboplatin, and etoposide) with or without rituximab.

Question 60: Was this donor used for any prior HCTs?

Indicate if the donor reported in question 31 was used for prior HCTs for this recipient. If this is the recipient's first HCT select "no." If this is an autologous infusion, select "no."

Question 61: Donor CMV-antibodies (IgG or Total) (Allogeneic HCTs only)

CMV is a common virus that infects 50-80% of adults worldwide, and is transmitted from person to person through bodily fluids. The virus that causes CMV is part of the herpes virus family and, like other herpes viruses, CMV may be dormant for a period of time before the virus is activated in the host. CMV infections are usually harmless in a healthy immune system and typically cause only mild symptoms, if any. However, if a person's immune system is seriously weakened (as in an immunosuppressed stem cell recipient) the virus can have serious consequences such as pneumonia, liver failure, and even death.

Most laboratory reports indicate a positive result as *reactive*, and a negative result as *non-reactive*. Occasionally, laboratory reports show a specific antibody titer. In this case, compare the laboratory result to the reported standards to determine if the result was reactive or non-reactive.

If the laboratory reports a CMV IgM antibody only, not total IgG/IgM or CMV IgG antibody; report the result as "not done."

If the laboratory reports the results as "inconclusive" or "equivocal," select "not done."

If the laboratory reports CMV testing by PCR (DNA detection), report the result as "not done." CMV testing by PCR is used to detect the presence of the CMV virus and does not test for prior exposure.

Indicate the test result documented on the laboratory report as either "reactive," "non-reactive," "not done," or "not applicable (cord blood unit)."

Question 62: Was plerixafor (Mozobil) given at any time prior to the preparative regimen? (Related HCTs only)

Stem cells do not typically circulate in the bloodstream. 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*. Indicate if the donor received plerixafor at any time prior to the start of stem cell collection.

Q63-70: Consent

To be compliant with Federal Regulations for human research subject protection, centers must obtain IRB-approved informed consent from recipients and donors (if applicable, for the related donor sample repository) to allow data submitted to the CIBMTR to be used for observational research. Informed consent must also be obtained from recipients and donors prior to submitting blood samples to the Research Sample Repository. The NMDP/CIMBTR has written protocols and informed consent documents for the Observational Database and Research Sample Repository. All centers must have local IRB approval for the Observational Database protocol. All centers that are NMDP member centers must also have local IRB approval for the Research Sample Repository protocol. With the exception of some selected sites (participating in the related sample repository), centers performing only related donor transplants and/or autologous transplants will not be submitting research samples and do not need to obtain local IRB approval for the repository protocol. The NMDP IRB has approved these protocols and consent forms, and the documents are provided to participating sites to include with their local IRB submissions.

International Centers must obtain consent of each patient participating in the Observational Database in a manner consistent with the laws and regulations of that country.

Under federal legislation, U.S. centers are required to submit outcomes data on all allogeneic transplants, related and unrelated. Data submitted without informed consent from the recipient should be reported on the TED Forms and will only be used for federally required research such as the center-specific outcomes analysis.

Question 63: Has the recipient signed an IRB-approved consent form for submitting research data to the NMDP/CIBMTR?

When a recipient consents to participate in the Observational Database, their data are contained in the CIBMTR's Observational Database and used for research. The database includes recipient baseline and outcome data for related and unrelated allogeneic transplants from any cell source, and for autologous transplants. Data are also collected on unrelated donors and their donation experiences.
The primary purpose of the Observational Database is to have a comprehensive source of data that can be used to study hematopoietic cellular transplantation. Studies using these data include:

- How well recipients recover from their transplants.
- How recovery after transplantation can be improved.
- What the long-term outcomes are after transplantation.
- How access to transplantation for different groups of recipients can be improved.
- How well donors recover from collection procedures.

- The application and success of transplantation in the management of marrow-toxic injuries.

Indicate if the recipient has signed an IRB-approved consent form to participate in the Observational Database. If “yes (patient consented),” continue with question 64. If “no (patient declined)” or “not applicable (patient not approached),” continue with question 65.

When to use the “Not Approached” option for the Research Database Consent
CIBMTR expects all transplant centers to approach all patients for the Research Database consent. The “not approached” option should only be used in the rare event when the physician feels it would be in the best interest of the patient not to be consented.

Recipients who transfer to another facility for a subsequent HCT
Any time a recipient transfers to another transplant center, an IRB approved research database consent would need to be obtained at the new center before data could be reported to the CIBMTR.

See the table below for additional information regarding how to report consent status for those with planned tandem or previous transplants.

Transplant Types	Instructions
Tandem Autologous Transplants	Most transplant centers would consider tandem autologous transplants as part of the same treatment plan and would consent the patient prior to the 1st HCT only. If that’s the case, the center should report “yes” to the consent question for the 2nd HCT and provide the date when the consent was first obtained.
Tandem Autologous-Allogeneic Transplants	Most transplant centers would consider tandem autologous-allogeneic transplants as part of the same treatment plan and would consent the patient prior to the 1st HCT only. If the center has one IRB approved consent covering both the autologous and allogeneic transplants, then the center should report “yes” to the consent question for the 2nd HCT and provide the date when the consent was first obtained. In the case where a center has separate research database consents for autologous and allogeneic HCTs, the center should obtain both consents from the patient prior to the 1st HCT. The center should then report “yes” to the consent question for the 2nd HCT & provide the date when the consent was first obtained.
Autologous HCT followed by subsequent autologous HCTs (not a tandem	In this scenario, CIBMTR does not require an additional consent form to be signed. The only consent required would be the one obtained at the time of the first autologous HCT. The center should report “yes” to the consent question for the subsequent HCT and provide the date when the consent was first obtained. However, a center’s IRB may require a second database consent form to be signed in this situation, and centers should refer to the higher standard set by their IRB.

autologous HCT)	
Allogeneic HCT followed by subsequent allogeneic HCTs (not a tandem allogeneic HCT)	In this scenario, CIBMTR does not require an additional consent form to be signed. The only consent needed would be the one obtained at the time of the first allogeneic HCT. The center should report "yes" to the consent question for the subsequent HCT and provide the date when the consent was first obtained. However, centers must follow their own institutional policy as well, which may require the patient be re-consented to the Research Database for a subsequent HCT.
Autologous HCT followed by subsequent allogeneic HCTs (not a tandem autologous HCT)	If the center has one IRB approved consent form covering both autologous and allogeneic transplants, then the center should report "yes" to the consent question for the 2nd HCT and provide the date when the consent was first obtained. In the case where a center has separate research database consent forms for autologous and allogeneic HCTs, the patient would need to be re-approached prior to the subsequent allogeneic transplant and asked to sign the appropriate consent form. If the patient was not asked to sign a 2nd consent form, then "not approached" must to be reported on the Pre-TED.

Question 64: Date form was signed:

Report the date the research database consent form was signed by the recipient. Do not report the date that the witness or health care professional signed the consent form.

Question 65: Did the recipient give permission to be directly contacted for future research?

Indicate if the recipient has given permission to be directly contact by the NMDP/CIBMTR for future research as documented on the research database consent form. If "yes (patient provided permission)," continue with question 66. If "no (patient declined)" or "not approached," continue with question 67.

Below is an example of this permission found in the NMDP/CIBMTR Research Database for Hematopoietic Cell Transplantation and Cellular Therapy Consent Form.

> *VIII. PERMISSION TO CONTACT FOR FUTURE CIBMTR RESEARCH STUDIES*
> Do you agree to give the CIBMTR permission to contact you in the future to tell you about research studies for which you are eligible? These studies are different from the studies that use your medical data. These studies would involve you directly, for example, asking you to complete a survey. You may decide if you want to participate in a specific study when you are contacted. By checking the "AGREE" box below, you are only agreeing that the CIBMTR can contact you to tell you about the study.
> Due to the need to follow up with you after your transplant, please tell your transplant center if your contact information changes. If the contact information on file is no longer valid, it might be necessary to

> use an internet-based search service to find you. By agreeing to be contacted for future studies, you authorize the CIBMTR to use such a service to search public and non-public information only for the purpose of trying to locate you.
>
> ☐ **I AGREE** to allow CIBMTR to contact me about future studies.
>
> ☐ **I DO NOT** want CIBMTR to contact me about future studies.

If the recipient declined to take part in the CIBMTR Research Database (as indicated in question 63) but gave permission to be contacted for future CIBMTR studies, ensure that there is documentation before selecting “yes.”

Question 66: Date form was signed:

Report the date the research database consent form was signed by the recipient. Do not report the date that the witness or health care professional signed the consent form.

Question 67: Has the recipient signed an IRB-approved consent form for submitting research blood samples to the NMDP/CIBMTR?

The Research Sample Repository contains blood samples from unrelated recipients and/or their adult volunteer donors or cord blood units. Related allogeneic recipients and/or donors will participate at selected transplant centers.
The primary objective of the Research Repository is to make blood samples available for research studies related to histocompatibility and hematopoietic cellular transplantation.

Studies in which these data may be used include:

- Improving the understanding of tissue matching for hematopoietic cellular donors and recipients.
- Determining and evaluating the factors that affect transplant outcomes.
- Studying the distribution of HLA tissue types in different populations (e.g., study tissue typing differences between different racial and ethnic populations to help develop methods to improve tissue matching between donors and recipients, including testing of rare HLA types).

Indicate if the recipient signed an IRB-approved consent form to donate research blood samples to the NMDP/CIBMTR. If “yes (patient consented),” continue with question 68. If “no (patient declined),” “not approached,” or “not applicable (center not participating),” continue with question 69.

Blood samples are not submitted for subsequent transplants, however, this question is asked for subsequent transplants. If the recipient previously consented to submit research blood samples to NMDP/CIBMTR, select “yes (patient consented).”

Question 68: Date form was signed:

Report the date the research sample consent form was signed by the recipient. Do not report the date that the witness or health care professional signed the consent form.

Question 69: Has the donor signed an IRB-approved consent form for submitting research blood samples to the NMDP/CIBMTR? (Related donors only)

Indicate if the donor signed an IRB-approved consent form to donate research blood samples to the CIBMTR. If “yes (donor consented),” continue with question 70. If “no (donor declined),” “not approached,” or “not applicable (center not participating),” continue with question 71.

Question 70: Date form was signed:

Report the date the research sample consent form was signed by the donor. Do not report the date that the witness or health care professional signed the consent form.

Q71-89: Product Processing/Manipulation

Question 71: Was the product manipulated prior to infusion?

If any part of the product was manipulated in any way prior to infusion at the transplant center, select "yes." **Do not report cryopreservation (including plasma removal as part of cryopreservation) as a method of manipulation; cryopreservation of the product(s) is reported on the 2006 form, if applicable.**

If the product was shipped to your facility, do not report manipulation of the product performed at the collection center.

If the product was not manipulated, select "no" and continue with question 90.

Question 72: Specify portion manipulated:

Indicate the portion of the product that was manipulated. If the entire product was manipulated, select "entire product" and continue with question 73. If a portion of the product was removed and manipulated, select "portion of product" and continue with question 73.

If different portions of the product were manipulated in different ways, select "portion of product" to indicate that the manipulation were not performed on the entire product.

Questions 73-89: Specify all methods used to manipulate the product:

Indicate the method(s) of stem cell manipulation. Answer each question as "yes" or "no" and do not leave any questions blank.

> **Steps in Manipulation**
> If the manipulation consists of several steps, individual steps do not need to be reported as separate manipulations. For example, washing that is part of CD34+ expansion does not need to be reported as a separate manipulation. Similarly, T-cell depletion that is part of expansion does not need to be reported. In the cases above, if T-cell depletion and/or washing are done as stand-alone manipulations, they should be reported.

Washed: Washing is performed to remove cryoprotectant (such as DMSO) from the product.

Diluted: Dilution is performed to reduce the cell concentration.[1]

Buffy coat enriched: Buffy coat enrichment is performed to reduce/remove mature erythrocytes and plasma.[1]

B-cell reduced: B cell reduction is performed to reduce/remove the quantity of B cells in the product.[1]

CD8 reduced: CD8 reduction is performed to reduce/remove the population of CD8 cells in the product.[1] The removal of CD8 cells may mitigate the risk of GVHD.

Plasma reduced (removal): Plasma reduction is performed to remove plasma via sedimentation or centrifugation.[1]

Plasma reduction may be done in order to minimize the risks associated with ABO mismatched products or to prevent volume overload. Previous versions of the Form 2006 made a distinction between plasma removal and volume reduction; for the purpose of this form, both volume reduction and plasma removal should be reported here.

Plasma reduction/removal that is part of the cryopreservation process should not be reported as manipulation.

RBC reduced: RBC reduction is performed to reduce/remove mature erythrocytes from the product.[1]

Cultured (ex-vivo expansion): Ex-vivo expansion is a method of culturing cells to “activate, expand, or promote development of a specified cell population in the presence of specific additive(s).”[1]

Genetic manipulation (gene transfer/transduction): Gene manipulation refers to any method used to modify the genes in the product cells. Gene transduction refers to the transfer of genes from one cell to another. Genetic manipulation is still in the early investigative phase of research.

PUVA treated: Product treated with psoralen and ultraviolet light (PUVA).[1]

CD34 enriched (CD34+ selection): CD34+ selection is a manipulation method also known as “positive selection.” This method identifies and selects stem cells that have a CD34+ marker on the cell surface.

CD133 enriched: CD133 enrichment identifies and selects stem cells that have a CD133 marker on the cell surface.

Monocyte enriched: Monocyte enrichment identifies and selects monocytes.

Mononuclear cells enriched: Mononuclear cell enrichment identifies and selects mononuclear cells.

T-cell depletion: T-cell depletion removes some or all of the T-cells in an effort to minimize GVHD. Methods of T-cell depletion include antibody affinity column, antibody-coated plates, antibody-coated plates and soybean lectin, antibody + toxin, immunomagnetic beads, and CD34 affinity column plus sheep red blood cell resetting.

If a method of manipulation was performed on the product, but is not listed above, select “yes” for question 88 and specify using question 89. Do not report cryopreservation (or processing used in the cryopreservation process) as manipulation.

[1] ISTB 128. *Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions.* ICCBBA ST-002. Version. 6.2. February 2015. Accessed at: http://www.iccbba.org/uploads/8f/18/8f18eb055d697857928a94e764eb8dc4/Standard-Terminology-for-Blood-Cellular-Therapy-and-Tissue-Product-Descriptions-v6.2.pdf Accessibility verified on March 5, 2015

Q90-93: Clinical Status of Recipient Prior to the Preparative Regimen (Conditioning)

Question 90: What scale was used to determine the recipient's functional status?

The CIBMTR uses the Karnofsky/Lansky scale to determine the functional status of the recipient immediately prior to the start of the preparative regimen. 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.

Questions 91-92: Performance score prior to the preparative regimen:

Recipient performance status is a critical data field that has been determined to be essential for all outcome-based studies. The CIBMTR uses the Karnofsky/Lansky scale to determine the functional status of the recipient immediately prior to the start of the preparative regimen. For the purposes of this manual, the term "immediately prior" represents the **pre-HCT work-up phase**, or **approximately one month** prior to the start of the preparative regimen. In cases where the pre-transplant work-up occurs in months prior to transplant (i.e., the pre-transplant workup occurs more than one month prior to transplant), a documented performance score may be submitted if the recipient does not have a score closer to the start of the preparative regimen, the recipient receives no additional treatment after the date of assessment, and the recipient's status does not clearly decline.

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 start of the preparative regimen. For an example of the Karnofsky/Lansky scale, see Appendix L.

If a Karnofsky/Lansky score is not documented in the source documentation (e.g., inpatient progress note, physician's clinic note), data management professionals **should not** assign a performance score based on analysis of available documents. Rather, a physician should provide documentation of the performance score.

The CIBMTR recognizes that some transplant centers prefer to collect 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 11 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. For centers that collect only an ECOG performance score, CIBMTR will make the following accommodations when auditing the source data:

- Centers collecting 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. This practice should be clear and reproducible.

For more information regarding converting an EGOG score to a Karnofsky/Lansky score, see Appendix L.

Question 93: Recipient CMV-antibodies (IgG or Total):

Report the cytomegalovirus (CMV) status of the recipient immediately prior to the start of the preparative regimen. For the purposes of this manual, the term “immediately prior” represents the **pre-HCT work-up phase**, or **approximately one month** prior to the start of the preparative regimen. An exception to this definition would apply to a recipient with a documented history of a “reactive” CMV test result. In this case, the CMV test may not be repeated during the pre-HCT work-up phase. Therefore a timeframe of greater than one month prior to the start of the preparative regimen is acceptable. In cases where the pre-transplant work-up occurs in months prior to transplant (i.e., the pre-transplant workup occurs more than one month prior to transplant), a CMV assessment may be submitted if the recipient does not have an assessment closer to the start of the preparative regimen.

CMV is a common virus that infects 50-80% of adults worldwide, and is transmitted from person to person through bodily fluids. The virus that causes CMV is part of the herpes virus family and, like other herpes viruses, CMV may be dormant for a period of time before the virus is activated in the host. CMV infections are usually harmless in a healthy immune system and typically cause only mild symptoms, if any. However, if a person’s immune system is seriously weakened (as in an immunosuppressed stem cell recipient) the virus can have serious consequences such as pneumonia, liver failure, and even death.

Most laboratory reports indicate a positive result as *reactive*, and a negative result as *non-reactive*. Occasionally, laboratory reports show a specific antibody titer. In this case, compare the laboratory result to the reported standards to determine if the result was reactive or non-reactive.

CMV antibody tested	Results	What to report on F2400 or F2000
IgG	Positive/reactive	Reactive
	Negative/non-reactive	Non-reactive
	Inconclusive	Inconclusive (or not done on F2400)
IgM	Positive/reactive	Reactive
	Negative/non-reactive	Not Done
	Inconclusive	Inconclusive (or not done on F2400)
Total IgG + IgM	Positive/reactive	Reactive

	Negative/non-reactive	Non-reactive
	Inconclusive	Inconclusive (or not done on F2400)

If the laboratory reports the results as “inconclusive” or “equivocal,” select “not done.”

Recipients < 6 months: If the recipient is less than 6 months old, report any positive CMV antibody results as “not done” due to the presence of maternal antibodies. However, in infants less than 6 months old, positive CMV PCR results indicate a CMV infection and the results may be reported as “reactive.”

Exposure to IVIG: Exposure to IVIG may result in a false positive CMV antibody result. If the recipient has been exposed to IVIG leading up to HCT (within 3-6 months), indicate the CMV antibody results using the following guidelines:

- If the recipient had a non-reactive CMV antibody result prior to IVIG therapy and then routine CMV PCR results showed no copies of CMV, the CMV antibody may be reported as “non-reactive,” even if the CMV antibody became reactive during IVIG treatment.
- If CMV PCR results quantified copies of CMV DNA (i.e., was positive) during IVIG treatment, the results may be reported as “reactive.”
- If the recipient did not have a CMV antibody test prior to the initiation of IVIG, but had a positive antibody test during the IVIG therapy, report “not done.”
- “Not done” should be reported if no CMV antibody tests were done prior to the initiation of IVIG therapy, even if CMV PCR testing was negative during IVIG treatment (because CMV PCR only detects active infection, not prior exposure).

For other situations, if the laboratory reports CMV testing by PCR (DNA detection) but no CMV antibody testing is done during the pre-transplant work-up or within one month prior to transplant, report the result as “not done.” CMV testing by PCR is used to detect the presence of the CMV virus and does not test for prior exposure.

Indicate the test result documented on the laboratory report as either “reactive,” “non-reactive,” or “not done.”

Q94-154: Comorbid Conditions

Question 94: Is there a history of mechanical ventilation?

A history of mechanical ventilation may impact the recipient's pulmonary function post-HCT. Mechanical ventilation is any assisted ventilation on behalf of the recipient. Mechanical ventilation can occur as both an endotracheal tube and ventilator, or as a BIPAP machine with a tight fitting mask in continuous use. The one exception to BIPAP is CPAP used for sleep apnea, which generally involves overnight use only for patients with documented sleep apnea. Therefore, **do not** report a CPAP used for sleep apnea, as it does not have the same implications as other forms of mechanical ventilation.

Indications for mechanical ventilation include, but are not limited to:

- Apnea with respiratory arrest (excludes sleep apnea)
- Acute lung injury
- Vital capacity < 15 mL/kg
- Chronic obstructive pulmonary disease (COPD)
- Clinical deterioration
- Respiratory muscle fatigue
- Obtundation or coma
- Hypotension
- Tachypnea or bradypnea

  If the recipient was placed on mechanical ventilation at any time prior to this HCT event (excluding mechanical ventilation during surgery) check "yes." If the recipient does not have a history of mechanical ventilation, check "no."

Question 95: Is there a history of proven invasive fungal infection?

Fungal infections play a major role in the clinical outcome of transplant recipients. For the purposes of this manual, the term "proven" is defined as a pathologic specimen or culture that yields a positive result. For example, a chest x-ray that reveals a nodule **is not** considered a "proven" diagnosis of aspergillus. A biopsy of a specimen with a positive culture for aspergillus **is** a proven diagnosis.

If the recipient has a history of **proven** invasive fungal infection at any time prior to this HCT, check "yes." If the recipient has not had a history of a proven invasive fungal infection, check "no." For a subsequent HCT, report any documented significant fungal infections in the recipient's medical history, starting with the preparative regimen of the previous HCT to the time prior to the preparative regimen for the current HCT.

Examples of proven invasive fungal infections include, but are not limited to: invasive aspergillosis, zygomycosis and other molds, invasive candidiasis, cryptococcosis, endemic mycosis, other yeasts, and pneumocystosis.
Non-invasive fungal infections such as thrush and nail fungus should not be reported.

For assistance with reporting fungal infections, consult a transplant physician.

Questions 96-133
Prior to answering question 96, review the list of co-existing disease(s) and/or organ impairments listed under questions 97-133.

Question 96: Were there clinically significant co-existing disease or organ impairment at the time of patient assessment prior to preparative regimen?

Hepatic and Renal Comorbidities[1]
In addition to the guidelines listed on the Pre-TED form, include the following time-specific guidelines when reporting hepatic and renal comorbidities
Hepatic Comorbidity: The assessment of liver function tests (ALT, AST and/or Total Bilirubin) has to include at least 2 values per test on two different days within a period extending between days -24 & -10 (or between days -40 & -10 if only a single value was reported between days -24 & day -10) before HCT.
Renal (Moderate/Severe) Comorbidity: Serum creatinine > 2 mg/dL or > 177 µmol/L, as detected in at least two lab values on two different days within a period extending between days -24 & -10 before HCT. The evaluation period may be extended to span between days -40 & -10 if the serum creatinine was only evaluated once between days -24 & -10; or on dialysis within a period of 4 weeks prior to transplant, or prior renal transplantation.

[1] Sorror, M. L. (2013). How I assess comorbidities before hematopoietic cell transplantation. *Blood*, 121(15), 2854-2863.

Report “yes” to question 96 if the recipient has a documented history and/or current diagnosis of any of the following:

Documented Medical History	Question Number
Arrythmia	97
Cardiac[2]	98
Cerebrovascular disease	99
Heart valve disease[3]	101

Inflammatory bowel disease	105
Peptic ulcer	107
Current Diagnosis at the Time of Pre-HCT Evaluation	**Question Number**
Rheumatologic	112
Solid tumor, prior[4]	113
Diabetes	100
Hepatic, mild[5]	102
Hepatic, moderate/severe	103
Infection	104
Obesity	106
Psychiatric disturbance	108
Pulmonary, moderate	109
Pulmonary, severe	110
Renal, moderate/severe[6]	111
Other (specify)	132 (133)

[2] Ejection fraction (EF) ≤ 50% should be reported only if present on most recent test

[3] Excluding asymptomatic mitral valve prolapse

[4] Excluding non-melanoma skin cancer, leukemia, lymphoma, or multiple myeloma

[5] Including any history of hepatitis B or hepatitis C infection

[6] Including renal transplantation at any time in the patient's history

The intent of this question is to identify serious pre-existing conditions that may 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 at the time of pre-HCT evaluation, or are in the recipient's medical history and could cause complications post-HCT. Conditions listed in the recipient's medical history that have been resolved (e.g., appendectomy), and/or that would not pose a concern during or after the HCT should not be reported.

Additionally, for the purposes of this manual, the term "at the time of patient assessment" is defined as the pre-HCT evaluation period prior to the start of the preparative regimen. If the recipient does not have a

documented history of clinically significant disease(s) or organ impairment(s), check “no” and continue with question 134.

For information regarding reporting clinically significant co-existing disease or organ impairment, see Appendix M.

Questions 97-133: Co-existing diseases or organ impairments

For each listed co-existing disease or organ impairment, check “yes,” “no,” or “unknown.”

Arrhythmia: Any history of atrial fibrillation or flutter, sick sinus syndrome, or ventricular arrhythmias requiring treatment.

Cardiac: Any history of coronary artery disease (one or more vessel coronary artery stenosis requiring medical treatment, stent, or bypass graft), congestive heart failure, myocardial infarction, or ejection fraction < 50% on the most recent test.

Cerebrovascular disease: Any history of transient ischemic attack, subarachnoid hemorrhage, or cerebrovascular accident.

Diabetes: Requiring treatment with insulin or oral hypoglycemics in the last 4 weeks but not diet alone

Heart valve disease: Except asymptomatic mitral prolapse.

Hepatic (mild): Chronic hepatitis, bilirubin > upper limit of normal to 1.5x upper limit of normal, or AST/ALT > upper limit of normal to 2.5x upper limit of normal, or any history of hepatitis B or hepatitis C infection. *See note in question 96.*

Hepatic (moderate/severe): Liver cirrhosis, bilirubin > 1.5x upper limit of normal, or AST/ALT > 2.5x upper limit of normal. *See note in question 96.*

Infection: Documented infection, fever of unknown origin, or pulmonary nodules requiring continuation of antimicrobial treatment after day 0.

Inflammatory bowel disease: Any history of Crohn’s disease or ulcerative colitis requiring treatment.

Obesity: Patients with a body mass index > 35 kg/m^2 or BMI-for-age ≥ 95% (pediatric recipients only) during pre-transplant work-up period.

Peptic ulcer: Any history of peptic ulcer confirmed by endoscopy and requiring treatment.

Psychiatric disturbance: Depression, anxiety, bipolar disorder, or schizophrenia requiring psychiatric consult or treatment in the last 4 weeks.

Pulmonary (moderate): Corrected diffusion capacity of carbon monoxide (e.g., DLCOc, DLCOcorr, DLCO) and/or FEV1 66-80% or dyspnea on slight activity at transplant.

Pulmonary (severe): Corrected diffusion capacity of carbon monoxide (e.g., DLCOc, DLCOcorr, DLCO) and/or FEV1 ≤ 65% or dyspnea at rest or requiring oxygen at transplant.

Renal (moderate/severe): Serum creatinine > 2 mg/dL or > 177 µmol/L, or on dialysis at transplant, or prior renal transplantation. *See note in question 96.*

Rheumatologic: Any history of systemic lupus erythematosus, rheumatoid arthritis, polymyositis, mixed connective tissue disease, or polymyalgia rheumatica requiring treatment (do NOT include degenerative joint disease, osteoarthritis)

Solid tumor (prior): Treated at any time point in the patient's past history, excluding non-melanoma skin cancer, leukemia, lymphoma, or multiple myeloma. For each listed prior solid tumor, check "yes" or "no." If "yes," enter the year of diagnosis of the corresponding solid tumor.

Other co-morbid condition: The "other, specify" category should be used to report co-morbid conditions that are of similar clinical concern as the other listed options. Chromosomal abnormalities, impairments and/or disorders associated with the primary disease should not be reported in this section, (e.g., Ph+ for CML/ALL recipients).

The physician performing the recipient's pre-HCT evaluation may use the HCT Co-Morbidity Index (HCT-CI) to document co-morbid conditions (see Appendix M).

Question 134: Was there a history of malignancy (hematologic or non-melanoma skin cancer) other than the primary disease for which this HCT is being performed?

The intent of this question is to identify other malignancies that may have an effect on the outcome of the HCT. A history of any benign tumor(s) should **not** be reported in this section. Malignancies reported in the previous solid tumor options should not be reported again here.

If the recipient is transplanted for a disease that has transformed from one disease to another, the original malignancy should **not** be reported in this section. Report the original malignancy as part of the appropriate disease subtype description in the Primary Disease for HCT section (questions 356-645). For more information regarding disease combinations and transformations, refer to the Common Disease Combinations and Common Disease Transformations tables in the Primary Disease for HCT section.

Indicate if there was a history of malignancy other than the disease for which this HCT is being performed.

Question 135-154: Specify which malignancy(ies) occurred:

For each listed prior malignancy, check “yes” or “no.” If “yes,” enter the year of diagnosis of the corresponding malignancy.

Use questions 152-154 to report any prior malignancies that were not listed in questions 135-150.

Q155-315: Pre-HCT Preparative Regimen (Conditioning)

Question 155: Height at initiation of pre-HCT preparative regimen:

Report the recipient's height just prior to the start of the preparative regimen. The intent of this question is to determine the height used when calculating preparative regimen drug doses. This height is usually documented on the transplant orders (for radiation and/or systemic therapy) or admitting orders. Report height to the nearest whole centimeter or inch (round up if 0.5 or greater).

Even if the recipient does not receive a preparative regimen, the height is still required.

Question 156: Actual weight at initiation of pre-HCT preparative regimen:

Report the recipient's actual body weight just prior to the start of the preparative regimen. The intent of this question is to report the actual weight at the time the preparative regimen starts (which may be different than the weight used to determine preparative regimen doses). This weight is usually documented on the transplant orders (for radiation and/or systemic therapy) or admitting orders. Report weight to the nearest whole kilogram or pound (round up if 0.5 or greater). Do not report adjusted body weight, lean body weight, or ideal body weight.

Even if the recipient does not receive a preparative regimen, the weight is still required.

Question 157: Was a pre-HCT preparative regimen prescribed?

Recipients are generally transplanted under a specific protocol that defines the radiation and/or systemic therapy the recipient is intended to receive as a preparative regimen. This protocol, which may be either a research protocol or standard of care protocol, should be referred to when completing this section.

However, there are instances when a preparative regimen is not given. Examples may include, but are not limited to:

- Primary diagnosis of an immune deficiency.
- Subsequent allogeneic HCT due to loss of, or poor, neutrophil engraftment.

If a preparative regimen is prescribed per protocol, check "yes" and continue with question 156. If a preparative regimen is not prescribed, check "no" and continue with question 316.

For more information regarding the recipient's preparative regimen, consult a transplant physician or contact your center's CIBMTR CRC.

Question 158: Classify the recipient's prescribed preparative regimen:

Myeloablative pre-transplant conditioning destroys bone marrow cells using high-dose radiation and/or systemic therapy. It is used to eliminate the recipient's immune system and to leave space in the bone marrow niche for the donated cells. A myeloablative regimen is sometimes used for recipients with non-malignant diseases who require HCT for marrow reconstitution (i.e., immunodeficiencies) or to produce a complete donor chimerism.

Non-myeloablative stem cell transplant (**NMA** or **NST**) and reduced-intensity conditioning (**RIC**) preparative regimens generally use lower doses of radiation and/or systemic therapy to prevent graft rejection and to suppress the recipient's hematopoietic immune system, but not eliminate it completely. Non-myeloablative protocols rely on the immune cells of the donor to destroy the disease (called graft versus tumor or GVT effect), and typically produces mixed chimerism. NST is a common treatment option for recipients who are older or who have other health problems, as the lower radiation and/or systemic therapy doses are easier for the recipient to tolerate.

In general, RIC includes any regimen that does not meet the criteria for either myeloablative or non-myeloablative regimens.

Based on the CIBMTR operational guidelines below, report if the regimen was myeloablative, reduced intensity, or non-myeloablative. The determination of whether the intent of the regimen was reduced intensity or non-myeloablative should be based either on the protocol at your center or the opinion of the physician overseeing the care of the recipient at your center. However, if there's a protocol utilized at your center that doesn't fall within CIBMTR operational guidelines for regimen intensity, you may report the regimen intensity based on the protocol intent.

Examples of Myeloablative, Reduced Intensity, and Non-Myeloablative Regimens

Myeloablative Regimens	Reduced Intensity and Non-Myeloablative Regimens
• TBI > 500 cGy (single) or > 800 cGy (fractionated) • Cyclophosphamide + TBI (> 500 cGy (single) or > 800 cGy (fractionated)) • Cyclophosphamide + Etoposide + TBI (> 500 cGy (single) or > 800 cGy (fractionated)) • Busulfan > 7.2 mg/kg IV or >9.0mg/kg orally • Busulfan >300 mg/m2 IV or >375 mg/m^2 orally • Busulfan (> 7.2 mg/kg IV or >9.0mg/kg orally) +	• TBI ≤ 500 cGy (single) or ≤ 800 cGy (fractionated) • ATG + Cyclophosphamide • BEAM (Carmustine [BCNU], Etoposide, Cytarabine [Ara-C], Melphalan) • Busulfan ≤ 7.2 mg/kg IV or ≤ 9.0mg/kg orally • Busulfan ≤ 300 mg/m^2 IV or ≤ 375 mg/m^2 orally • Melphalan ≤ 150 mg/m^2

Cyclophosphamide • Busulfan (>7.2 mg/kg IV or >9.0 mg/kg orally) + Melphalan >150 mg/m^2 • Melphalan >150 mg/m^2 • Thiotepa ≥ 10 mg/kg • Treosulfan > 30,000 mg/m^2 or > 30 g/m^2	• Fludarabine + Cytarabine • Fludarabine + Cyclophosphamide • Fludarabine + TBI ≤ 500 cGy (single) or ≤ 800 cGy (fractionated) • Thiotepa < 10 mg/kg • Treosulfan ≤ 30,000 mg/m^2 or ≤ 30 g/m^2 • Etoposide + Cyclophosphamide

! These values represent the total prescribed doses. For example, if a recipient is scheduled to receive Melphalan 100 mg/m^2 for two days (200 mg/m^2), the regimen would be myeloablative because the total prescribed dose is > 150 mg/m^2.

Indicate whether the intent of the preparative regimen was “myeloablative” (to produce marrow ablation or pancytopenia), “non-myeloablative,” or “reduced intensity.”

Question 159: Date pre-HCT preparative regimen began (irradiation or drugs):

Enter the date the preparative regimen began. Use the earliest date from questions 163, (radiation), or 170-236, 253-311 (systemic therapy) and 314. Additional radiation and/or intrathecal chemotherapy start dates may be prior to the date the preparative regimen began.

Question 160: Was irradiation planned as part of the pre-HCT preparative regimen?

If irradiation is planned as part of the preparative regimen, check “yes” and continue with question 161. If irradiation is not planned, check “no” and continue with question 168. Irradiation performed as previous treatment should not be reported in this section. Report irradiation performed as previous treatment on the appropriate Disease Specific Form.

Question 161: What was the prescribed radiation field?

Indicate if the planned irradiation was to “total body,” “total body by tomotherapy,” “total lymphoid or nodal regions,” or “thoracoabdominal region.”

Question 162: Total prescribed dose:

Enter the total dose of radiation prescribed. If radiation was prescribed as a single dose, the amount of radiation delivered in the single dose constitutes the total dose. If the radiation was prescribed in fractionated doses, multiply the dose per fraction by the total number of fractions to determine the total dose. Enter the total dose of radiation in either grays (Gy) or centigrays (cGy).

Example:
Radiation Order: TBI, 200 cGy/day for three days (3 doses)
Total dose: 200 cGy x 3 doses = 600 cGy
Report "Total Dose" as: 600 cGy

Question 163: Date started:

Enter the date the single dose or first fraction of radiation was administered.

Question 164: Was the radiation fractionated?

Radiation is either delivered as a single dose or in several treatments (fractions). Radiation is fractionated to increase the loss of diseased cells, as they do not recover as quickly as disease-free cells.

If the radiation was fractionated, check "yes" and continue with question 165. If the radiation was not fractionated, check "no" and continue with question 168.

Question 165: Prescribed dose per fraction:

Enter the prescribed dose per fraction in either grays (Gy) or centigrays (cGy).
The dose per fraction multiplied by the total number of fractions (question 167) must be equal to the total dose reported in question 162.

Question 166: Number of days:

Enter the total number of days radiation therapy was prescribed, including any days of rest between days when therapy was administered. The number of days radiation was administered can be greater than the number of fractions.

Example:
Radiation Order: TBI, 200 cGy/day every other day (Mon-Wed-Fri) x 3 doses
Total dose: 200 cGy x 3 doses = 600 cGy
Report "Number of days" as: 5

Question 167: Total number of fractions:

Enter the total number of fractions (treatments) of radiation that were administered. The recipient may receive more than one fraction per day (hyperfractionation).

The total number of fractions multiplied by the dose per fraction (question 165) must be equal to the total dose reported in question 162.

Questions 168-315: Drugs

! The following questions report the prescribed drug therapy that was part of the preparative regimen. Do not report the dose that was actually given. If the recipient has comprehensive report forms due, the actual dose given will be reported on the Recipient Baseline Form (Form 2000). **Do not include drugs that are intended to offset the side effects of the chemotherapy** (e.g., corticosteroids for nausea, MESNA for hemorrhagic cystitis, etc.).

* Occasionally, protocols list drugs that may be given before and after day 0. If the drugs are planned to be given before and after day 0, only the doses given before day 0 should be quantified in the preparative regimen section. The doses given after day 0 should be reported in the Post-HCT Disease Therapy Planned as of Day 0 or GVHD Prophylaxis section. For example, if bortezomib or rituximab is planned to be given on Days -2, +1, +4, and +7, report the Day -2 dose in the preparative regimen section, and the post-transplant doses as planned post-HCT therapy.

* For ATG, Campath, and Cyclophosphamide: If these agents are given for GVHD prophylaxis both prior to and after Day 0, they must be reported in separate sections of the Pre-TED form. Report doses given prior to Day 0 in the preparative regimen section of the Pre-TED (questions 168-315). If given after Day 0 as GVHD prophylaxis, report in the GVHD prophylaxis section of the Pre-TED (questions 316-341).

* In this section, include any intrathecal drugs the recipient received for prophylaxis or treatment of CNS disease within 14 days prior to the start date of the preparative regimen.

* The form lists each drug by the generic name. The form also lists some drugs by broad categories, with specific drugs listed individually. For example, anthracycline is listed as the broad drug category, followed by the specific drugs daunorubicin, doxorubicin, and idarubicin. The following website provides the trade names under which generic drugs are manufactured: http://www.rxlist.com/script/main/hp.asp.

Report the ***total* dose** of each drug as **prescribed** in the preparative regimen section of the HCT protocol. **Do not report the prescribed *daily* dose**. Drug doses must be reported in whole numbers. If the total dose includes a decimal, round to the nearest whole number. For paper submission, do not modify the number of boxes or include decimal values. The pharmacy record or Medication Administration Record (MAR) should be used for determining the date the drug was started.

Report the dose units as either "mg/m^2," "mg/kg," "target total AUC (µmol x min/L)," "mCi," or "MBq." If the total prescribed dose is reported in a unit other than those listed, convert the dose to the appropriate unit. See the example below or consult with a transplant pharmacist for the appropriate conversion. If drug doses cannot be converted to the unit listed (e.g., Campath), leave the unit field blank, override the error (using "unable to answer"), and attach a copy of the source document to the Pre-TED using the Log of Appended Documents (Form 2800).

Example: Calculating Total Drug Doses
Drug doses are calculated either by recipient weight in kilograms (kg) or recipient body surface area (BSA) in m^2. The HCT protocol will specify "x mg/kg" or "x mg/m^2" and the total number of doses to be administered.
For example, if the protocol requires cyclophosphamide at 60 mg/kg x 2 days (i.e., 2 doses), the "total prescribed dose" should be reported as "120 mg/kg."

Pharmacokinetic testing can be used to determine whether the drug concentration in the bloodstream is appropriate to the dose given. This reflects the speed of absorption and elimination of the drug. These tests are usually performed using the first dose of systemic therapy, or a test dose, where multiple samples are drawn at specific time points following the first dose. The samples are sent to a laboratory that performs the testing to determine the drug concentration. If carboplatin was prescribed, indicate if pharmacokinetic testing was performed to determine the preparative regimen dosing. If it is not known whether or not this testing was performed, consult a transplant physician.

A common example of this situation occurs in the use of busulfan. In some cases, a "test dose" of the drug is given before the actual preparative regimen is started, and this dose is used for acquiring drug levels that are used to adjust the dose that will be used in the preparative regimen. In other situations, the first dose of the drug is given in the usual fashion as part of the preparative regimen. After this first dose, serum drug levels are drawn and sent to a reference lab. The drug is continued at the starting dose until the lab results are reported and adjustment is made to later doses.

When a drug is used for the preparative regimen where pharmacokinetics will be tested, it is important to distinguish whether the testing will be done with a "test dose" before beginning the preparative regimen or using the first dose of the preparative regimen. The reporting of the dosing for the CIBMTR forms depends upon this distinction. This helps distinguish whether the dose is part of the therapeutic regimen, or not.

1. A test dose was given **> 24 hours** prior to the intended therapeutic dosing.
    - **Example:** A patient with AML underwent allogeneic HCT from a sibling; busulfan and cyclophosphamide were used as the preparative regimen. The patient presented to clinic 9 days before the HCT, where a dose of busulfan at 0.5 mg/kg was given intravenously. Blood samples

were drawn for the next 6 hours, after which the patient left the clinic. His samples were sent to a lab, results were returned the next day, and an adjusted dose of busulfan was calculated. He returned to the hospital 6 days before HCT, and began to receive busulfan at the adjusted dose intravenously for 4 days, followed by cyclophosphamide, and proceeded to receive his cells. Since he received 0.5 mg/kg as a "test dose," this would not be reported in his total preparative regimen dose.

If a test dose was given, where the dose was distinct from the therapeutic dosing preparative regimen (often 1-2 or more days prior to the initiation of regular dosing), the following should be reported:

- On the Pre-TED (2400) form, the total prescribed dose per protocol would NOT include the test dose.
- On the Baseline (2000) form, the start date of the chemotherapy agent should be reported as the date the first therapeutic dose was administered. The actual dose received would NOT include the test dose.

2. The first dose of therapeutic dosing is used for monitoring.
    - **Example:** A patient with MDS received an allogeneic HCT from an unrelated donor; busulfan and fludarabine were used as the preparative regimen. She was admitted to the hospital 7 days before her HCT, and received a dose of busulfan at 0.8 mg/kg IV at 6:00 AM. Serum samples were drawn every 30 minutes until the next dose of Busulfan at 0.8 mg/kg IV was given at 12:00 noon. Her blood was sent to a reference lab, and she continued to receive busulfan every 6 hours. On day -6, the lab called with her drug levels, and it was determined that the current dose was correct. No adjustment was made, and she completed all 16 doses of busulfan. Since the dose of busulfan (0.8 mg/kg) that was used for drug testing was ALSO her first dose of the preparative regimen, it should be included in the amount of drug that was given for preparative regimen. The total prescribed dose per protocol should be reported as "13 mg/kg." (0.8 mg/kg x 16 doses = 12.8 mg/kg rounded to 13 mg/kg).

      If the first dose of the preparative regimen was used to determine pharmacokinetics, the following should be reported:

      - On the Pre-TED (2400) form, the total prescribed dose per protocol would include the dose used for monitoring.
      - On the Baseline (2000) form, the start date of the chemotherapy agent should be reported as the date the first dose was administered. The actual dose received would include the dose used for monitoring.

Test doses must be reported consistently at your center. Since most centers follow a consistent approach to pharmacokinetic testing, it should be straightforward for the center to adopt a consistent approach to the reporting of test doses.

The “other, specify” category should be used only if the drug is not one of the listed options. If more than one “other” drug is prescribed, list the name of the drugs in the space provided **and** attach a copy of the source document to the Pre-TED using the Log of Appended Documents (Form 2800).Do not report additional sites of radiation (e.g., cranial boost) in the “other” drug category. If the recipient is assigned to the Comprehensive Report Forms by the form selection algorithm, the additional sites of radiation will be reported on the Recipient Baseline Form (Form 2000). If the recipient is assigned to TED Forms by the form selection algorithm, the additional sites of radiation will not be reported.

If the Pre-TED is being completed for a subsequent HCT, do not report therapy that was given to treat the recipient’s disease (between the previous and current planned HCTs) in the preparative regimen section.

If there is a change to the chemotherapy preparative regimen (e.g., from busulfan + fludarabine to melphalan + fludarabine) after the Form 2400 has been submitted, an error correction must be completed in FormsNet to update the chemotherapy regimen given.

Q316-341: GVHD Prophylaxis

! The following GVHD prophylaxis questions are to be completed for allogeneic HCTs only. Autologous and syngeneic HCTs continue with question 342.

✻ For ATG, Campath, and Cyclophosphamide: If these agents are given for GVHD prophylaxis both prior to and after Day 0, they must be reported in separate sections of the Pre-TED form. Report doses given prior to Day 0 in the preparative regimen section of the Pre-TED (questions 168-315). If given after Day 0 as GVHD prophylaxis, report in the GVHD prophylaxis section of the Pre-TED (questions 316-341).

Question 316: Was GVHD prophylaxis planned/given?

After allogeneic HCT, specific immunosuppressive therapy may be administered to prevent GVHD or to immunosuppress the host marrow, thereby promoting engraftment of the donor stem cells. Most transplant centers have specific GVHD prophylaxis protocols and graft rejection protocols. **Planned** agents a recipient received as a result of these protocols should be included in this section.

If GVHD prophylaxis was planned per protocol, check “yes” and continue with question 317. If GVHD prophylaxis was not planned per protocol, check “no” and continue with question 342.

Questions 317-341: Specify:

The prophylactic drug options listed on the form are intended to be administered in a **systemic or oral form**. If the recipient received one of the listed drugs in a topical form, report the drug in the “other, specify” category.

Do not report T-cell depletion of the product or drugs administered after the onset of GVHD.

The Pre-TED Form lists the generic chemotherapy drug names. The following website provides the trade names under which generic drugs are manufactured: http://www.rxlist.com/script/main/hp.asp

If GVHD prophylaxis is used for a syngeneic (monozygotic or identical twin) or autologous HCT, attach a copy of the source document to the Pre-TED using the Log of Appended Documents (Form 2800).

Q342: Other Toxicity Modifying Regimen

Question 342
The following other toxicity modifying regimen question is optional for non-U.S. centers.

Question 342: Was KGF (palifermin, Kepivance) started or is there a plan to use it?

Check “yes” if KGF was started or planned. Check “no” if KGF was not started or planned.

Check “masked trial” if the recipient is part of a KGF study where the agent the recipient received is not known (e.g., placebo, drug, or other agent). Use the error correction process to update the data field once the trial is over and the agent the recipient was given is known.

Q343-355: Post-HCT Disease Therapy Planned as of Day 0

Question 343: Is this HCT part of a planned multiple (sequential) graft/HCT protocol?

If the current HCT is part of a planned multiple graft/HCT protocol, check “yes.” The HCT for which the form is being completed could be for any of the transplants within the planned multiple graft/HCT protocol. The word “planned” **should not** be interpreted as: *if the recipient relapses, then the “plan” is to perform a subsequent HCT*. If this HCT is not part of a planned multiple graft/HCT protocol, check “no.”

Question 344: Is additional post-HCT therapy planned?

If additional post-HCT therapy is planned according to the protocol or standard of care, check “yes” even if the recipient does not receive the planned therapy. The word “planned” **should not** be interpreted as: *if the recipient relapses, then the “plan” is to treat with additional therapy*. If additional post-HCT therapy is not planned per protocol, check “no” and continue with question 356.

Questions 345-355
The following post-HCT planned therapy questions are optional for non-U.S. centers.

Questions 345-355: Additional post-HCT planned therapy

Indicate if the options listed on the form are intended to be part of the post-HCT planned therapy according to the protocol or standard of care. Report other planned therapies in the “other, specify” category.

Q356-357: Primary Disease for HCT

Disease Classification Questions

The newest versions of the TED Forms use the World Health Organization (WHO) disease classifications. The Disease Classification questions contain all of the established WHO disease types and subtypes. The "other, specify" category should be used only if the recipient's disease is not one of the listed options. For more information regarding disease classification, consult a transplant physician, contact your center's CIBMTR CRC, or visit the WHO website at: http://www.who.int/classifications/icd/en/.

Several of the Disease Classification questions ask for "Status at Transplantation." Although there are many interpretations of disease response criteria, **when reporting data to the CIBMTR, use the guidelines in this manual to determine disease status**. A majority of the disease response criteria are established by an international working group. Citations of resources used to define disease responses are included where applicable.

If the recipient's status is unclear, consult with the transplant physician for further information or contact your center's CIBMTR CRC.

Malignant vs. Non-Malignant

Malignant diseases involve cells dividing without control that can spread to other parts of the body through blood and lymph systems. These diseases are usually characterized by unlimited, aggressive growth, invasion of surrounding tissues, and metastasis.

Non-malignant diseases involve cell overgrowth, but lack the malignant properties of cancer.

The CIBMTR database disease codes are represented in parentheses after the disease subtype on the Disease Classification questions and can be helpful in mapping diagnosis [e.g., Myeloid Sarcoma (295)], and determining if the disease is malignant or non-malignant. Disease codes (10-299) indicate a malignant disease, with the exception of Paroxysmal Nocturnal Hemoglobinuria (PNH) (56). A disease code of (300) or above indicates a non-malignant disease, with the exception of disease code (900), which could indicate either a malignant or non-malignant disease.

If the indication for HCT is due to a combination of diseases or a transformation of one disease to another, it may be necessary to report multiple disease classifications. The tables below list how common examples of disease combinations and transformations should be reported using the Disease Classification questions.

Common Disease Combinations[1]

Disease Combinations	Report Primary Disease as:	Report disease diagnosis date of:	Complete multiple disease sections of the Pre-TED?
FAN or SAA and AML	AML	AML	No
FAN or SAA and MDS	MDS	MDS	No
MYE and AMY	MYE	MYE	No

Common Disease Transformations[1]

Disease Transformation	Report primary disease as:	Report disease diagnosis date of:	Complete multiple disease sections on the Pre-TED?
MDS or MPS to AML	AML	AML	Yes- AML and MDS/MPN
JMML to AML	AML	AML	Yes- AML and MDS/MPN (select questions only)
NHL to another NHL	Second NHL diagnosis	First NHL diagnosis	No
HL to NHL[2]	NHL	HL	No
CLL to NHL (i.e., Richter's Syndrome)	NHL	CLL	Yes- Other Leukemias and NHL

[1] AML=Acute Myelogenous Leukemia; AMY=Amyloidosis; CLL=Chronic Lymphocytic Leukemia; FAN=Fanconi Anemia; MDS=Myelodysplastic Syndrome; MPS=Myeloproliferative Disease; MYE=Multiple Myeloma; NHL=Non-Hodgkin Lymphoma; SAA=Severe Aplastic Anemia.

[2] Ensure that the disease process is a transformation from Hodgkin lymphoma to Non-Hodgkin lymphoma (typically diffuse large B-cell lymphoma), rather than the distinct entity "B-cell lymphoma, unclassifiable, with features indeterminate between DLBCL and classical Hodgkin Lymphoma."

Question 356: Date of diagnosis for primary disease for HCT:

The date of diagnosis is important because the interval between diagnosis and HCT is often a significant indicator for the recipient's prognosis post-HCT.

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease. Enter the date the sample was collected for examination. If the diagnosis was determined at an outside center,

and no documentation of a pathological or laboratory assessment is available, the dictated date of diagnosis within a physician note may be reported. Do not report the date symptoms first appeared.

If the recipient was diagnosed prenatally (*in utero*), report the date of birth as the date of diagnosis.

If the exact pathological diagnosis date is not known, use the process described in General Instructions, Guidelines for Completing Forms.

If this is a subsequent HCT for a new malignancy (or other new indication), report the date of diagnosis of the new malignancy.

Question 357: What was the primary disease for which the HCT was performed?

From the list provided, select the primary disease for which the recipient is receiving the HCT and continue with the appropriate disease classification questions

- Q359-418: Acute Myelogenous Leukemia
- Q419-461: Acute Lymphoblastic Leukemia
- Q462-465: Other Acute Leukemia
- Q466-479: Chronic Myelogenous Leukemia
- Q480-572: Myelodysplastic (MDS)/Myeloproliferative (MPN) Diseases
- Q573-579: Other Leukemia
- Q580-582: Hodgkin Lyphoma
- Q583-588: Non-Hodgkin Lymphoma
- Q589-620: Multiple Myeloma/Plasma Cell Disorder
- Q621-622: Solid Tumors
- Q623-624: Severe Aplastic Anemia
- Q625-627: Inherited Abnormalities of Erythrocyte Differentiation or Function
- Q628-630: Disorders of the Immune System
- Q631-632: Inherited Abnormalities of Platelets
- Q633-634: Inherited Abnormalities of Metabolism
- Q635-636: Histiocytic Disorders
- Q637-644: Autoimmune Diseases
- Q645: Other Disease

Q358-418: Acute Myelogenous Leukemia (AML)

Acute Myelogenous Leukemia (AML) is a cancer of the white blood cells. It is characterized by the rapid proliferation of abnormal, immature myelocytes, known as myeloblasts, in the bone marrow. This accumulation of blasts in the marrow prevents the formation of healthy red blood cells, white blood cells, and/or platelets. Normal myeloblasts develop into neutrophils, basophils, and eosinophils, which are all white blood cells that fight infection. In AML, the leukemic myeloblasts do not fully develop and are unable to fight infection. The symptoms of AML result from a drop in red blood cell, platelet, and normal white blood cell counts caused by the replacement of normal bone marrow with leukemic cells.

Certain prognostic indicators are associated with poorer outcomes. These include advanced age (50+ years of age), AML arising from MDS or secondary/therapy-related AML, and certain genetic mutations that are described in greater detail later in this manual.

Question 358: Specify the AML classification

Indicate the disease classification at diagnosis; the older FAB classifications are shown in parenthesis, e.g., (M0).

Report the most specific entity that applies to the recipient. For example, if the recipient was classified using both cytogenetic data and the M5 FAB classification, the more specific cytogenetic data should be reported for classification purposes.

Question 359: Did AML transform from MDS or MPN?

AML often evolves from MDS or MPN. This transformation is typically distinguished by the percentage of blasts in the bone marrow.
AML that transforms from MDS or MPN has a lower survival prognosis because of the association with unfavorable cytogenetic abnormalities.

AML can also evolve from Juvenile Myelomonocytic Leukemia (JMML). JMML is a rare form of chronic leukemia that affects young children, usually before the age of five. JMML results from DNA mutations in cells called monocytes. Normal monocytes attack invading microorganisms and assist lymphocytes in carrying out immune functions. Abnormal monocytes in JMML accumulate in the bone marrow and interfere with the production of normal white blood cells, red blood cells, and platelets.

If AML transformed from MDS or MPN (including JMML), check “yes” and complete both the **AML and MDS/MPN** disease classification sections (questions 480-572). If AML did not transform from MDS or MPS, check “no.”

If MDS/MPN is suspected, but not confirmed by documented laboratory or pathologic findings, or if there is documentation of MDS/MPN **concurrent** with AML, check “no.”

Question 360: Was disease (AML) therapy related?

Agents such as radiation or systemic therapy used to treat other diseases (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, or breast cancer) can damage the marrow and lead to a secondary malignancy such as AML. If the diagnosis of AML is therapy-related, check “yes.”

If the diagnosis of AML is not therapy-related, check “no.”

- If AML was preceded by therapy-related MDS, check “no.”
- If the recipient developed AML after an environmental exposure (e.g., exposure to benzene), check “no.”

If it is unknown whether or not the diagnosis of AML was therapy-related, check “unknown.”

Question 361: Did the recipient have a predisposing condition?

A predisposing condition is a condition that contributes to the susceptibility of developing leukemia. Therefore, diagnosis of the condition increases the likelihood that the recipient will develop leukemia. If the recipient has a documented history of a predisposing condition, check “yes” and continue with question 362. If there is no history of a predisposing condition or if predisposition is unknown, indicate “no” or “unknown” and continue with question 364.

Questions 362-363: Specify condition:

Bloom syndrome is an autosomal recessive genetic disorder characterized by excessive chromosome breakage and corresponding rearrangements, proportional dwarfism, and sun sensitivity. The chromosomal instability seen in Bloom syndrome is generally assumed to be responsible for these individuals’ predisposition to malignancy.

Down syndrome is also a chromosomal disorder (trisomy 21). It is characterized by an additional chromosome 21. Down syndrome patients exhibit a particular set of facial characteristics, growth deficiency, and cognitive impairment. Although Down syndrome patients have a reduced risk of developing many common malignancies, they have an increased risk of developing leukemia.

Fanconi anemia is a rare genetic blood disorder that prevents the body from producing a sufficient number of new blood cells to function properly. Abnormal blood cells may also be produced. These patients are short in stature, exhibit skeletal anomalies, and have an increased risk of developing solid tumors and leukemias.

Neurofibromatosis type 1, also known as von Recklinghausen disease, is an autosomal dominant genetic disorder characterized by mutation of chromosome 17 resulting in the inactivation of the *NF1* gene. This results in abnormal growth and proliferation of neural crest cells. Patients with neurofibromatosis type 1 often have multiple neurofibromas (benign neural tumors), skeletal abnormalities, café au lait spots, Lisch nodules, freckling in the axilla or groin, and/or optic nerve glioma. Patients with biallelic inactivation of *NF1* may have an increased risk of developing malignant neoplasms, including rhabdomyosarcoma, pheochromocytoma, and, in children, myelodysplastic syndrome and acute leukemia.

Indicate the recipient's predisposing condition prior to the diagnosis of leukemia. If the condition was "other," specify the condition in question 363.

Question 364: Were cytogenetics tested (conventional or FISH)?

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient's disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix R, Cytogenetic Abbreviations and Terminology.

Examples of AML Cytogenetic Findings Categorized by Prognosis

Favorable	Intermediate	Poor
t(15;17) t(8;21) inv(16) or t(16;16)	Normal +8 t(9;11) *All other abnormalities*	≥ 3 abnormalities 5- or 5q- 7- or 7q- t(9;22)

Indicate if cytogenetic studies were obtained at any time prior to the start of the preparative regimen.

If cytogenetic studies were obtained, check "yes" and continue with question 365.

If cytogenetic studies were not obtained or it is unknown if chromosome studies were performed, indicate "no" or "unknown" and continue with question 402.

Question 365: Results of tests:

If cytogenetic studies identified abnormalities (any karyotype other than 46XX or 46XY), indicate "abnormalities identified" and continue with question 366.

If cytogenetic studies yielded "no evaluable metaphases" or there were "no abnormalities" identified, continue with question 402.

Questions 366-401: Specify cytogenetic abnormalities identified at any time prior to the start of the preparative regimen:

If question 365 indicates that abnormalities were identified, each of questions 366-400 must be answered as "yes" or "no." Do not leave any response blank. Indicate "yes" for each cytogenetic abnormality identified at any time prior to the start of the preparative regimen. Indicate "no" for all options not identified by cytogenetic assessment at any time prior to the start of the preparative regimen. For cases where AML has transformed from MDS, only report "yes" for cytogenetic abnormalities identified on or after the date of diagnosis for AML. If one or more abnormalities are best classified as "other abnormality," specify in question 401.

If ≥ 3 cytogenetic abnormalities were identified at any time prior to the start of the preparative regimen, select "yes" for question 399 (complex, ≥ 3 distinct abnormalities) and specify the corresponding abnormalities in questions 366-398. If any of these abnormalities are not listed among 366-398, report "other abnormality," and specify in question 401. For example, if the karyotype included -7, +8, and -13, report "yes" for questions 367, 373, 399, and 400-401. Complete the remaining indicators as "no" and do not leave any response blank.

Question 402: Were tests for molecular markers performed (e.g., PCR)?

Molecular assessment involves testing blood or bone marrow for the presence of known molecular markers associated with the recipient's disease. Molecular assessments are the most sensitive test for genetic abnormalities and involve amplifying regions of cellular DNA by polymerase chain reaction (PCR), typically using RNA to generate complementary DNA through reverse transcription (RT-PCR). The amplified DNA fragments are compared to a control, providing a method of quantifying log increase of genetic mutation transcripts. Each log increase is a 10-fold increase of gene transcript compared to control.

Indicate if molecular studies were obtained at any time prior to the start of the preparative regimen.

If molecular studies were obtained, check "yes" and continue with question 403.

If molecular studies were not obtained or it is not known if molecular studies were performed, indicate "no" or "unknown" and continue with question 412.

Questions 403-411: Specify molecular markers identified at any time prior to the start of the preparative regimen:

If question 402 indicates that tests for molecular markers were performed, then each of questions 403-410 must be answered as “positive,” “negative,” or “not done.” Do not leave any response blank. If tests identified a molecular marker other than those listed in questions 403-409, use question 410 to report it. If question 410 is answered “positive” or “negative,” specify the other molecular marker in question 411.

Common Molecular Markers Associated with AML

Molecular Abnormality	Characteristics
CEBPA	CEBPA, aka CCAAT/enhancer binding protein α, is a transcription factor required for the differentiation of granulocytes. Numerous CEBPA mutations have been identified in relation to AML, with the majority of patients displaying biallelic mutations ultimately resulting in the down regulation of gene activity. Decreased gene activity results in decreased differentiation potential for immature granulocytes. An estimated 7-15% of AML patients have CEBPA mutations and CEBPA mutations are generally found in M1 and M2 subtypes in conjunction with intermediate-risk cytogenetics. Studies show an association with more favorable outcomes.[1]
FLT3-D835 point mutation	FLT3 encodes a receptor tyrosine kinase. The FLT3-D835 point mutation, aka FLT3-TKD, is an activating mutation impacting tyrosine-kinase domains. FLT3 mutations are found in up to 1/3 of all AML patients. The clinical significance of TKD activation remains unclear. FLT3-D385 mutations are often found in conjunction with other mutations. Overall, FLT3-D385 is not considered a favorable or poor prognostic indicator. However, in certain combinations with other mutations, there are associations with both improved and diminished survival.[23]
FLT3-ITD mutation	FLT3 encodes a receptor tyrosine kinase. The FLT3-ITD (internal tandem duplication) interferes with certain down regulation functions within receptor tyrosine kinases, leading to activation of TK activity. FLT3 mutations are found in up to 1/3 of all AML patients. FLT3-ITD is considered a poor prognostic factor. Sorafenib (Nexavar) has been shown to initially improve disease response in FLT3-ITD-positive AML.[4]
IDH1	Isocitrate Dehydrogenase (IDH) is an oxidative enzyme involved in the citric acid cycle. IDH1 mutations result in incorrect catalytic activity, leading to increased levels of an oncometabolite, 2-hydroxyglutarate. The pathologic activity of IDH1 mutations is still being studied, but it has been suggested that IDH mutations may be a distinct mechanism in AML pathogenesis; research models show they may cause an accumulation of hematopoietic progenitor cells. Early research suggests IDH1 mutation may be a less favorable prognostic indicator.[5]
IDH2	Isocitrate Dehydrogenase (IDH) is an oxidative enzyme involved in the citric acid cycle. IDH2 is a mitochondrial homolog to IDH1. Much like IDH1 mutations, IDH2 mutations result in incorrect catalytic activity, leading to increased levels of (D)-2-hydroxyglutarate. The pathologic activity of IDH2 mutations are still being studied, but it has been suggested that IDH mutations may be a distinct mechanism in AML pathogenesis; research models show they may cause an accumulation of hematopoietic progenitor cells. Early research suggests IDH2 mutation may be a more favorable prognostic indicator, unlike IDH1 mutation, though there may be differences based on where the IDH2 mutation occurs in gene.[6]

KIT	KIT encodes a receptor tyrosine kinase. The KIT mutations at exons 8 and 17 are associated with activation of encoded proteins, resulting in activation impacting tyrosine-kinase domains. Patients with t(8;21) and inv(16) cytogenetics are frequently screened for KIT mutations, which adversely affect prognosis in these patients.[7]
NPM1	NPM1 encodes a protein responsible for multiple cellular functions, including the regulation of the ARF-p53 tumor suppressor pathway. Mutations in NPM1 result in gene over-expression and subsequent inactivation of ARF-p53 tumor suppression pathway. NPM1 mutations are one of the most common molecular markers seen in AML and are associated with improved survival.[8]
Other molecular marker	Assessments for other molecular markers known or believed to be associated with AML may be performed. If these studies are performed, indicate “positive” or “negative” and specify the marker in question 411. If another molecular marker was not performed, select “not done.”

[1] Lin L, Chen C, Lin D, Tsay W, Tang J, Yeh Y, Shen H, Su F, Yao M, Huang S, Tien H. (2005). Characterization of CEBPA Mutations in Acute Myeloid Leukemia: Most patients with CEBPA mutations have biallelic mutations and show a distinct immunophenotype of the leukemic cells. *Clin Cancer Res*, 11, 1372-9.

[2] Mead AJ, Linch DC, Hills RK, Wheatley K, Burnett AK, Gale RE. (2007). FLT3 tyrosine kinase domain mutations are biologically distinct from and have a significantly more favorable prognosis than FLT3 international tandem duplications in patient with acute myeloid leukemia. *Blood*, 110, 1262-70.

[3] Whitman SP, Ruppert AS, Radmacher, MD, et al. (2008). FLT3 D835/I836 mutations are associated with poor disease-free survival and a distinct gene-expression signature among younger adults with de novo cytogenetically normal acute myeloid leukemia lacking FLT3 internal tandem duplications. *Blood*, 111, 1552-59.

[4] Man CH, Fung TK, Ho C, et al. (2011). Sorafenib treatment of FLT-ITD+ acute myeloid leukemia: favorable initial outcome and mechanisms of subsequent non-responsiveness associated with the emergence of a D835 mutation. *Blood*, 119 (22), 5133-43.

[5] Marucci G, Maharry K, Wu YZ, et al. (2010). IDH1 and IDH2 Gene Mutations Identify Novel Molecular Subsets Within De Novo Cytogenetically Normal Acute Myeloid Leukemia: A Cancer and Leukemia Group B Study. *J Clin Oncol*, 28(14), 2348-55.

[6] Green CL, Evans CM, Zhao L, et al. (2011).The prognostic significance of IDH2 mutations in AML depends on the location of the mutation. *Blood*, 118(2), 409-12.

[7] Döhner K, Döhner H. (2008).Molecular characterization of acute myeloid leukemia. *Haematologica*, 93(7), 976-82.

[8] Varhaak RGW, Goudswaard CS, van Putten W, et al. (2005).Mutations in nucleophosmin (NPM1) in acute myeloid leukemia (AML): association with other gene abnormalities and previously established gene expression signatures and their favorable prognostic significance. *Blood*, 106(12), 3747-54.

Question 412: What was the disease status (based on hematologic test results)?

Indicate the disease status of AML at the last assessment prior to the start of the preparative regimen. **See AML Response Criteria for disease status definitions.**

Question 413: How many cycles of induction therapy were required to achieve CR?

Chemotherapy is initially given as induction therapy intended to bring the disease into remission. Recipients usually have one to two cycles of induction therapy; disease prognosis is considered less favorable if the patient fails to achieve remission with the first induction therapy and even poorer if patients fail two or more induction therapies.[1] An example of a common induction therapy for all AML subtypes (except M3) is a combination of an anthracycline and cytarabine, commonly known as "7+3." In this regimen, cytarabine is typically administered for seven days at a dose of 100 mg/m^2/day. The anthracycline (usually daunorubicin at 45 to 60 mg/m^2/day or idarubicin at 12 mg/m^2/day) is generally given on the first three days the cytarabine is given.

The second phase of chemotherapy is known as consolidation therapy. The goal of consolidation therapy is to destroy any remaining leukemia cells and sustain remission. An example of a common consolidation therapy for all AML subtypes (except M3) is high-dose cytarabine, commonly referred to as "HiDAC." In this regimen, cytarabine is typically administered at a dose exceeding 10 g/m^2 per cycle.

Maintenance chemotherapy may follow consolidation therapy. Maintenance chemotherapy is given in lower doses and is intended to prolong a remission. Maintenance therapy is used less commonly for the treatment of AML than other malignancies. Treatment may also be administered for relapsed disease. Much like induction therapy, treatment for relapse is intended to bring the disease back into remission. Systemic therapeutic agents used to induce remission following relapse often differ from those used in the initial induction, since the disease is often resistant to many of the agents used earlier in the disease course and is considered high-risk with a poor prognosis. Allogeneic HCT is often considered the only potential "cure" for relapsed disease.

Indicate the number of cycles of induction therapy that were required to achieve the first CR.

[1] Ravandi F, Cortes J, Faderl S, et al. (2010). Characteristics and outcome of patients with acute myeloid leukemia refractory to one cycle of high-dose cytarabine-based induction therapy. *Blood*, 116(26):5818-23.

Question 414: Was the recipient in molecular remission?

Molecular assessment involves testing blood or bone marrow for the presence of known molecular markers associated with the recipient's disease. Molecular assessments are the most sensitive test for genetic

abnormalities and involve amplifying regions of cellular DNA by polymerase chain reaction (PCR), typically using RNA to generate complementary DNA through reverse transcription (RT-PCR).

Molecular remission is a treatment response in which no minimal residual disease in the blood and/or marrow can be detected by molecular methods (e.g., PCR).

If molecular abnormalities associated with the recipient's disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate "yes."

If molecular abnormalities associated with the recipient's disease were identified at the last evaluation prior to the start of the preparative regimen, indicate "no."

Indicate "unknown" if molecular abnormalities associated with the recipient's disease were identified previously and no molecular assessment was performed prior to the start of the preparative regimen.

Indicate "not applicable" if one of the following applies:

- No molecular assessments were performed at any time prior to the start of the preparative regimen.
- Molecular abnormalities associated with the recipient's disease were not identified on previous testing and no molecular abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Question 415: Was the recipient in remission by flow cytometry?

Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tissue preparations for multiple unique cell characteristics. Its primary clinical purpose in the setting of leukemias is to quantify blasts in the peripheral blood or bone marrow, or to identify unique cell populations through immunophenotyping. Flow cytometry assessment may also be referred to as "MRD," or minimal residual disease, testing.

Flow cytometric remission is a treatment response in which no blasts can be detected.

If flow cytometric abnormalities associated with the recipient's disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate "yes."

If flow cytometric abnormalities associated with the recipient's disease were identified at the last evaluation prior to the start of the preparative regimen, indicate "no."

Indicate "unknown" if flow cytometric abnormalities associated with the recipient's disease were identified previously and no flow cytometry assessment was performed prior to the start of the preparative regimen.

Indicate “not applicable” if one of the following applies:

- No flow cytometry assessments were performed at any time prior to the start of the preparative regimen.
- Flow cytometric abnormalities were not identified on previous testing and no flow cytometric abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Question 416: Was the recipient in cytogenetic remission?

Cytogenetic assessment involves testing blood or bone marrow for the presence of a known cytogenetic abnormalities that reflect the recipient’s disease. FISH is categorized with cytogenetics. Although often used for finding specific features in DNA, FISH is not as sensitive as molecular methods, even though the markers identified may be the same.

Cytogenetic remission is a treatment response where **both** of the following criteria are met:

- The karyotype reverts to normal, and
- There are no clonal chromosomal abnormalities detected in the blood and/or marrow.

If cytogenetic abnormalities associated with the recipient’s disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate “yes.”

If cytogenetic abnormalities associated with the recipient’s disease were identified at the last evaluation prior to the start of the preparative regimen, indicate “no.”

Indicate “unknown” if cytogenetic abnormalities associated with the recipient’s disease were identified previously and no cytogenetic assessment was performed prior to the start of the preparative regimen.

Indicate “not applicable” if one of the following applies:

- No cytogenetic assessments were performed at any time prior to the start of the preparative regimen.
- Cytogenetic abnormalities were not identified on previous testing and no cytogenetic abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Continue with question 418.

Question 417: Date of most recent relapse:

Enter the date of the most recent relapse prior to the start of the preparative regimen. If reporting a pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear), enter the date the sample was collected. If extramedullary disease was detected by radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place. If the physician determines cytogenetic or molecular relapse, enter the date the sample was collected for cytogenetic or molecular evaluation. If the physician determines evidence of relapse following a clinical assessment during an office visit, report the date of assessment.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 418: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q419-461: Acute Lymphoblastic Leukemia (ALL)

Acute Lymphoblastic Leukemia (ALL) is a cancer of the white blood cells. It is characterized by the rapid proliferation of abnormal, immature lymphocytes, known as lymphoblasts, in the bone marrow. This accumulation of blasts in the marrow prevents the formation of healthy red blood cells, white blood cells and/or platelets. Normal lymphoblasts develop into B and T lymphocytes that fight infection. In ALL, the leukemic lymphoblasts do not fully develop and therefore cannot fight infection. The symptoms of ALL are caused by the replacement of normal bone marrow with leukemic cells, resulting in. a drop in red blood cells, platelets, and normal white blood cells. It is estimated that 80-85% of ALL cases occur in children, with peak incidence of pediatric ALL at age 5. Biologically, adult and pediatric ALL are very different. Pediatric cases are more often characterized by favorable prognostic indicators including a precursor B-cell population, TEL/AML1 fusion gene, and/or hyperdiploidy; adult cases are more often characterized by poor prognostic indicators including a precursor T-cell population and/or BCR/ABL fusion gene.[1]

[1] Sallan S. Myths and Lessons from the Adult/Pediatric Interface in Acute Lymphoblastic Leukemia. *ASH Education Book*, 1st edition. 2006:128-32.

Question 419: Specify ALL classification

Indicate the disease classification at diagnosis.

Due to the aggressive nature of precursor T- and precursor B-cell lymphoblastic lymphoma (or lymphoma/leukemia), the primary disease reported for recipients with these malignancies should be acute lymphoblastic leukemia (T-cell lymphoblastic leukemia/lymphoma or B-cell ALL, NOS {L1/L2}).

If the cytogenetic or molecular abnormalities present at diagnosis are listed on the Pre-TED form, check the sub-type rather than “B-cell ALL, NOS” option.

Question 420: Were tyrosine kinase inhibitors (i.e., imatinib mesylate) given for pre-HCT therapy at any time prior to the start of the preparative regimen?

! There is currently an issue on this form. Question 420 should say “e.g. imatinib mesylate.” Report any tyrosine kinase inhibitors, rather than just imatinib mesylate.

Report if the recipient received any tyrosine kinase inhibitors (TKI). Examples of TKIs include Imatinib mesylate (Gleevec, Glivec, STI-571, or CGP57148B), dasitinib (Sprycel), and nilotonib. Indicate “yes” or “no.”

Question 421: Were cytogenetics tested (conventional or FISH)?

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods include conventional chromosome analysis (karyotyping) or fluorescence in situ hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix R, Cytogenetic Abbreviations and Terminology.

Examples of ALL Cytogenetic Findings Categorized by Prognosis (Adult Precursor B-cell ALL)[2]

Favorable	Intermediate	Poor	Very Poor
High hyperdiploidy (51-65 chromosomes)	Normal 11q abnormalities del(6q) del(17p) del(9p) del(12p) -13/del(13q) t(14q32) t(10;14) Low hyperdiploidy (47-50 chromosomes) Tetraploidy (> 80 chromosomes) -7/ del(7p)	+8 11q23 abnormalities/ MLL t(1;19) t(17;19) t(5;14) t(9;22)	≥ 5 abnormalities t(4;11) t(8;14)

[2] Pullarkat V, Slovak ML, Kopecky KJ, Forman SJ, Appelbaum FR. Impact of cytogenetics on the outcome of adult acute lymphoblastic leukemia: results of Southwest Oncology Group 9400 study. *Blood*. 2008;111(5):2563-72.

Indicate if cytogenetic studies were obtained at any time prior to the start of the preparative regimen.

If cytogenetic studies were obtained, check “yes” and continue with question 422.

If cytogenetic studies were not obtained, or if it is unknown if chromosome studies were performed, indicate “no” or “unknown” and continue with question 450.

Question 422: Results of test

If cytogenetic studies identified abnormalities (any karyotype other than 46XX or 46XY), indicate "abnormalities identified" and continued with question 423.

If cytogenetic studies yielded "no evaluable metaphases" or there were "no abnormalities" identified, continue with question 450.

Questions 423-449: Specify abnormalities

If question 422 indicates that abnormalities were identified, each of questions 423-448 must be answered as "yes" or "no." Do not leave any response blank. Indicate "yes" for each cytogenetic abnormality identified at any time prior to the start of the preparative regimen in questions 423-448; indicate "no" for all options not identified on cytogenetic assessment at any time prior to the start of the preparative regimen. If one or more abnormalities are best classified as "other abnormality," specify in question 449.

If ≥ 3 cytogenetic abnormalities are identified at any time prior to the start of the preparative regimen, select "yes" for question 447 (complex, ≥ 3 distinct abnormalities) and specify the corresponding abnormalities in questions 423-446. If any of these abnormalities are not listed among 423-446, report "other abnormality," and specify in question 449. For example, if the karyotype included -7, +8, and -13, report "yes" for questions 423, 425, 447, and 448-449. Answer the remaining questions "no" and do not leave any response blank.

Question 450: Were tests for molecular markers performed (e.g., PCR)?

Molecular assessment involves testing blood or bone marrow for the presence of known molecular markers associated with the recipient's disease. Molecular assessments are the most sensitive test for genetic abnormalities and involve amplifying regions of cellular DNA by polymerase chain reaction (PCR), typically using RNA to generate complementary DNA through reverse transcription (RT-PCR). The amplified DNA fragments are compared to a control, providing a method of quantifying log increase of genetic mutation transcripts. Each log increase is a 10-fold increase of gene transcript compared to control.

Indicate if molecular studies were obtained at any time prior to the start of the preparative regimen.

If molecular studies were obtained, check "yes" and continue with question 451.

If molecular studies were not obtained or it is not known if molecular studies were performed, indicate "no" or "unknown" and continue with question 455.

Questions 451-454: Specify abnormalities

If question 450 indicates that tests for molecular markers were performed, then each of questions 451-453 must be answered as “positive,” “negative,” or “not done.” Do not leave any response blank. If question 453 is answered “positive” or “negative,” specify the molecular marker identified in question 454.

Common Molecular Markers Associated with ALL

Molecular Abnormality	Characteristics
BCR-ABL	BCR-ABL, *aka* Philadelphia chromosome, refers to the tyrosine kinase gene fusion resulting from the translocation of material from chromosome 9 (ABL) onto chromosome 22 (BCR). Molecular weight varies depending on exact location of the translocation; isoform p190 is typically seen in ALL. Tyrosine kinase inhibitor therapies such as imatinib mesylate (Gleevec) target and block ABL from fusing with BCR. Presence of BCR-ABL gene fusion is associated with poorer outcomes.[3]
TEL-AML/AML1	TEL-AML1, *aka* ETV6-RUNX1, is a fusion gene resulting from the translocation of chromosomes 12 and 21. It is the most common fusion gene seen in childhood precursor B-cell ALL. Research in murine models shows that cell lines expressing TEL-AML1 proliferate more slowly than the non-expressing cell lines, but evade inhibition of proliferation typically regulated by tissue growth factor ß (TGF-ß), ultimately leading to the growth of the leukemic cell population. TEL-AML1 is considered a favorable prognostic indicator.[4][5]
Other molecular marker	Assessments for other molecular markers known or believed to be associated with ALL may be performed. If these studies were performed, indicate “positive” or “negative” and specify the marker in question 454. If another molecular marker was not performed, select “not done.”

[3] Wassmann B, Pfeifer H, Scheuring UJ, et al. (2004). Early prediction of response in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ALL) treated with imatinib. *Blood*, 103(4):1495-8.

[4] Ford AM, Palmi C, Bueno C, et al. (2009). The TEL-AML1 leukemia fusion gene dysregulates the TGF-ß pathway in early B lineage progenitor cells. *J Clin Invest*, 119(4):826-36.

[5] Jamil A, Kahwash S, Ruymann FB, Klopfenstein KJ. (2000). TEL/AML-1 fusion gene: its frequency and prognostic significance in childhood acute lymphoblastic leukemia. *Cancer Genet Cytogenet*, 122(2):73-8.

Question 455: What was the disease status (based on hematological test results)?

Indicate the disease status of ALL at the last assessment prior to the start of the preparative regimen. **See ALL Response Criteria for disease status definitions.**

Question 456: How many cycles of induction therapy were required to achieve CR?

Chemotherapy is initially given as induction therapy intended to bring the disease into remission. Recipients usually have one to two cycles of induction therapy. An example of a common induction therapy for precursor B-cell ALL in children with higher-risk prognostic indicators is a combination of vincristine, prednisone, an anthracycline, and L-asparaginase given over 4-6 weeks. Patients with a rapid response, defined as < 5% blasts within 7 to 14 days of starting induction, have improved outcomes.[6]

The second phase of chemotherapy is known as consolidation therapy. The goal of consolidation therapy is to destroy any remaining leukemia cells and sustain remission. An example of a consolidation therapy for precursor B-cell ALL in children is daunorubicin and cytarabine; several studies support the use of consolidation therapy in ALL.

Maintenance therapy typically involves daily doses of mercaptopurine and weekly doses of methotrexate. Treatment continues for 2-3 years for most children with ALL. Treatment may also be administered for relapsed disease. Much like induction therapy, treatment for relapse is intended to bring the disease back into remission. Systemic therapeutic agents used to induce remission following relapse often differ from those used during initial induction, since the disease is considered high-risk with a poor prognosis and is often resistant to many of the agents used earlier in the disease course. Allogeneic HCT is often considered the only potential “cure” for relapsed disease, if the patient has not already been transplanted.

Indicate the number of cycles of induction therapy that were required to achieve the first CR.

[6] Gaynon PS, Desai AA, Bostrom BC, et al. Early response to therapy and outcome in childhood acute lymphoblastic leukemia: a review. *Cancer*. 1997;80(9):1717-26.

Question 457: Was the recipient in molecular remission?

Molecular assessment involves testing blood or bone marrow for the presence of known molecular markers associated with the recipient’s disease. Molecular assessments are the most sensitive test for genetic abnormalities and involve amplifying regions of cellular DNA by polymerase chain reaction (PCR), typically using RNA to generate complementary DNA through reverse transcription (RT-PCR).

Molecular remission is a treatment response in which no minimal residual disease in the blood and/or marrow can be detected by molecular methods (e.g., PCR).

If molecular abnormalities associated with the recipient’s disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate “yes.”

If molecular abnormalities associated with the recipient's disease were identified at the last evaluation prior to the start of the preparative regimen, indicate "no."

Indicate "unknown" if molecular abnormalities associated with the recipient's disease were identified previously and no molecular assessment was performed prior to the start of the preparative regimen.

Indicate "not applicable" if one of the following applies:

- No molecular assessments were performed at any time prior to the start of the preparative regimen.
- Molecular abnormalities were not identified on previous testing and no molecular abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Question 458: Was the recipient in remission by flow cytometry?

Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tissue preparations for multiple unique cell characteristics. Its primary clinical purpose in the setting of leukemias is to quantify blasts in the peripheral blood or bone marrow, or to identify unique cell populations through immunophenotyping. Flow cytometry assessment may also be referred to as "MRD," or minimal residual disease, testing.

Flow cytometric remission is a treatment response in which no blasts can be detected.

If flow cytometric abnormalities associated with the recipient's disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate "yes."

If flow cytometric abnormalities associated with the recipient's disease were identified at the last evaluation prior to the start of the preparative regimen, indicate "no."

Indicate "unknown" if flow cytometric abnormalities associated with the recipient's disease were identified previously and no flow cytometry assessment was performed prior to the start of the preparative regimen.

Indicate "not applicable" if one of the following applies:

- No flow cytometry assessments were performed at any time prior to the start of the preparative regimen.
- Flow cytometric abnormalities were not identified on previous testing and no flow cytometric abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Question 459: Was the recipient in cytogenetic remission?

Cytogenetic assessment involves testing blood or bone marrow for the presence of known cytogenetic abnormalities that reflect the recipient's disease. FISH is categorized with cytogenetics. Although often used for finding specific features in DNA, FISH is not as sensitive as molecular methods, even though the markers identified may be the same.

Cytogenetic remission is a treatment response where **both** of the following criteria are met:

- The karyotype reverts to normal, and
- There are no clonal chromosomal abnormalities detected in the blood and/or marrow.

If cytogenetic abnormalities associated with the recipient's disease were identified previously, but the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate "yes."

If cytogenetic abnormalities associated with the recipient's disease were identified at the last evaluation prior to the start of the preparative regimen, indicate "no."

Indicate "unknown" if cytogenetic abnormalities associated with the recipient's disease were identified previously and no cytogenetic assessment was performed prior to the start of the preparative regimen.

Indicate "not applicable" if one of the following applies:

- No cytogenetic assessments were performed at any time prior to the start of the preparative regimen.
- Cytogenetic abnormalities were not identified on previous testing and no cytogenetic abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Continue with question 461.

Question 460: Date of most recent relapse:

Enter the date of the most recent relapse prior to the start of the preparative regimen. If reporting a pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear), enter the date the sample was collected. If extramedullary disease was detected by radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place. If the physician determines cytogenetic or molecular relapse, enter the date the sample was collected for cytogenetic or molecular evaluation. If the physician determines evidence of relapse following a clinical assessment during an office visit, report the date of assessment.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 461: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q462-465: Other Acute Leukemia

Questions 462-463: Specify other acute leukemia classification

Indicate the other acute leukemia disease classification at diagnosis. If the subtype is not listed, report as "other leukemia" and specify the reported disease.

- Acute undifferentiated leukemia is a type of AML characterized by immature predominating cells that cannot be classified.
- Biphenotypic, bilineage, or hybrid leukemias have characteristics representative of both myeloid and lymphoid lineages.
- Mast cell leukemia is characterized by an increased number of tissue mast cells in the peripheral blood.

Question 464: What was the disease status (based on hematological test results)?

Indicate the disease status of acute leukemia at the last evaluation prior to the start of the preparative regimen.

Primary Induction Failure (PIF)
The patient received treatment for acute leukemia but never achieved complete remission at any time. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in complete remission.

Complete Remission (CR)
Hematologic complete remission is defined as meeting all of the following response criteria for at least four weeks.

- < 5% blasts in the bone marrow
- Normal maturation of all cellular components in the bone marrow
- No extramedullary disease (e.g., CNS, soft tissue disease)
- Neutrophils ≥ 1,000/µL
- Platelets ≥ 100,000/µL
- Transfusion independent

In some cases, there may not be a four-week interval between completion of therapy and the pre-transplant disease assessment; in this case, CR should still be reported as the status at transplant, since

it represents the “best assessment” prior to HCT. This is an exception to the criteria that CR be durable beyond four weeks; the pre-transplant disease status should not be changed based on early relapse or disease assessment post-transplant.

Include recipients with persistent cytogenetic or molecular abnormalities who meet the above CR criteria for hematologic CR.

Include recipients meeting the above CR criteria regardless of how many courses of therapy were required to achieve CR.

The number of this complete remission can be determined by using the following guidelines:

- 1st CR: no prior relapse
- 2nd CR: one prior relapse
- 3rd or higher: two or more prior relapses

Relapse (REL)
Relapse is defined as the recurrence of disease after CR, meeting the following criteria:

- ≥ 5% blasts in the marrow or peripheral blood
- Extramedullary disease
- Reappearance of cytogenetic and/or molecular abnormalities associated with diagnosis that, in the judgment of a physician, are at a level representing relapse
- Disease presence determined by a physician upon clinical assessment

The number of this relapse can be determined by using the following guidelines:

- 1st relapse: one prior CR
- 2nd relapse: two prior CRs
- 3rd or higher: three or more CRs

Do not include a partial response (PR) when determining number of relapse. Recipients who achieve a PR to treatment should be classified as either PIF or relapse; PR in acute leukemia is generally of short duration and is unlikely to predict clinical benefit.

No Treatment
The recipient was diagnosed with acute leukemia and never received therapeutic agents; include patients who have received only supportive therapy, including growth factors and/or blood transfusions.

Question 465: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q466-479: Chronic Myelogenous Leukemia (CML)

Chronic myelogenous leukemia (CML) is a slow-progressing cancer of the myeloid white blood cells. It is characterized by increased proliferation of immature white blood cells (granulocytes) with damaged DNA, or blasts, which accumulate in the blood and bone marrow. Normal blasts develop into white blood cells that fight infection. The symptoms of CML are caused by the replacement of normal bone marrow with leukemic cells, resulting in fewer red blood cells, platelets, and normal white blood cells.

Question 466: Specify CML classification

Indicate the CML disease classification at diagnosis. The WHO disease classification requirements state that a diagnosis of CML must include the following: Philadelphia chromosome, complex variation and/or variant form, or BCR/ABL gene rearrangement (see Table 11 below). Evidence of these chromosomal abnormalities may be found at any time between diagnosis and the start of the preparative regimen.

Report the combination that best describes the chromosomal abnormalities. If none of the listed abnormalities are identified, but CML is suspected, report under “Myelodysplastic (MDS)/Myeloproliferative (MPN)” and indicate “Atypical chronic myeloid leukemia” as the detailed disease classification (questions 480, 577, and 579).

CML Classification Requirements

Term	Definition
Philadelphia chromosome t(9;22)(q34;q11)	An exchange of genetic material between region q34 of chromosome 9 and region q11 of chromosome 22.
Complex variation	Translocation of three or more chromosomes, one of which must be chromosome 22 [e.g., t(3; 9; 22)].
Variant form	Any translocation involving 22q11, or 22.q11.2 in which CML is the suspected diagnosis [e.g., t(13; 22)(p3;q11)].

Question 467: Did recipient receive treatment prior to this HCT?

If the recipient received therapy to treat CML prior to this HCT, check “yes” and continue with question 468. If the recipient did not receive therapy to treat CML, check “no” and continue with question 474.

Questions 468-473: CML treatment

Indicate the therapy the recipient received to treat CML prior to this HCT. If the recipient's treatment consisted of a combination of chemotherapeutic agents, check the "combination chemotherapy" box **and** each drug included in the combination from the list provided. The "other, specify" category should only be used if the drug is not one of the listed options. For example, if the recipient received a combination of interferon and cytarabine, check all of the following: "combination chemotherapy," "interferon," and "other, specify: cytarabine."

Questions 474: What was the disease status at last evaluation prior to the start of the preparative regimen?

Indicate the disease status of CML at the last evaluation prior to the start of the preparative regimen.

Complete Hematologic Remission (CR) *If yes, also complete questions 475-479.*
A treatment response where all of the following criteria are met:

- White blood count is < 10 × 10^9/L, without immature granulocytes and with < 5% basophils
- Platelet count < 450 × 10^9/L
- Non-palpable spleen

Chronic Phase *If "first," also complete question 479. If "second or greater," complete questions 478-479.*
Characterized by relatively few blasts (<10%) present in the blood and bone marrow. Symptoms are often not present. The chronic phase may last several months to years, depending on the recipient and the treatment they receive.

Accelerated Phase *If yes, also complete questions 478-479.*
One or more of the following must be present:

- 10%-19% blasts in blood or marrow
- ≥ 20% basophils in peripheral blood
- Clonal marrow cytogenetic abnormalities in addition to the single Philadelphia chromosome (clonal evolution)
- Increasing spleen size, unresponsive to therapy
- Increasing WBC, unresponsive to therapy
- Thrombocytopenia (platelets < 100,000), unrelated to therapy
- Thrombocytosis (platelets > 1,000,000), unresponsive to therapy

Blast Crisis *If yes, also complete questions 478-479.*
Characterized by having ≥ 20% blasts (formerly ≥ 30%) in the peripheral blood or bone marrow. Having extramedullary blastic infiltrates (i.e., myeloid sarcoma, granulocytic sarcoma, or chloroma) also qualifies as blast phase. The red cell, platelet, and neutrophil counts may decrease and episodes of infection and bleeding may result. Symptoms such as fatigue, shortness of breath, abdominal pain, bone pain, and spleen enlargement may occur. Blast crisis is similar to acute leukemia in its signs and its effects on the recipient, and can involve lymphoid or myeloid lineages (so-called lymphoid blast crisis or myeloid blast crisis).

Question 475: Cytogenetic complete remission (Ph negative)

Cytogenetic response is determined by either conventional or FISH cytogenetics for the Philadelphia chromosome [t(9;22)].

Cytogenetic responses are divided into several categories:

Complete	Ph+	0%
Partial	Ph+	1%-35%
Minor	Ph+	36%-65%
Minimal	Ph+	66%-95%
None	Ph+	> 95%

If the recipient had a *complete cytogenetic* response at the last evaluation prior to the start of the preparative regimen, indicate “yes.”

If the recipient had a *partial, minor, minimal, or none* cytogenetic response at the last evaluation prior to the start of the preparative regimen, indicate “no.”

Indicate “unknown” if one of the following applies:

- No cytogenetic assessments were performed at any time prior to the start of the preparative regimen.
- The Philadelphia chromosome associated with the recipient’s disease was identified previously and no cytogenetic assessment was performed prior to the start of the preparative regimen.
- The Philadelphia chromosome associated with the recipient’s disease was not identified by previous testing and no cytogenetic abnormalities were identified at the last evaluation prior to the start of the preparative regimen.

Question 476: Molecular complete remission (BCR-ABL negative)

PCR testing reveals no molecular evidence of the BCR-ABL fusion gene in the blood (e.g., BCR-ABL transcript is non-detectable and non-quantifiable in an assay that has at least 4-5 log range of detection).

Molecular remission is a treatment response in which no minimal residual disease in the blood and/or marrow can be detected by molecular methods (e.g., PCR).

If the BCR-ABL fusion gene associated with the recipient's disease was identified previously and the criteria above were met at the last evaluation prior to the start of the preparative regimen, indicate "yes."

If the BCR-ABL fusion gene associated with the recipient's disease was identified at the last evaluation prior to the start of the preparative regimen, indicate "no."

Indicate "unknown" if one of the following applies:

- No molecular assessments for the BCR-ABL fusion gene were performed at any time prior to the start of the preparative regimen.
- The BCR-ABL fusion gene associated with the recipient's disease was identified previously, but no molecular assessment was performed prior to the start of the preparative regimen
- The BCR-ABL fusion gene associated with the recipient's disease was not identified by previous testing and the BCR-ABL fusion gene was not identified at the last evaluation prior to the start of the preparative regimen.

Question 477: CML disease status before treatment that achieved this CR

From the options listed below, indicate the disease status of CML immediately prior to the treatment that achieved this complete hematologic remission. For definitions of chronic phase, accelerated phase, and blast phase, see question 474 above.

Question 478: Number

Indicate the number of the disease phase reported in question 474.

Question 479: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical

examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q480-572: Myelodysplastic (MDS) / Myeloproliferative (MPN) Diseases

✻ If the recipient is being transplanted for AML that has transformed from MDS/MPN, the primary disease for HCT must be reported as AML. Disease Classification questions must be completed for both AML and MDS/MPN.

The **myelodysplastic syndromes (MDS)** are a group of clonal hematopoietic stem cell diseases characterized by cytopenia(s), dysplasia (abnormal growth or development leading to an alteration in size, shape, and organization of the cell) in one or more of the major myeloid cell lines (WBC, RBC, and/or platelets), ineffective hematopoiesis, and an increased risk of developing acute myelogenous leukemia (AML). MDS occurs primarily in older adults, with a median age of 70 years. The majority of patients present with symptoms related to cytopenias. Most patients present with anemia requiring RBC transfusions.

Primary or *de novo* MDS occurs without a known history of chemotherapy or radiation exposure. Some inherited hematologic disorders, such as Fanconi anemia, dyskeratosis congenita, Shwachmann-Diamond syndrome, and Diamond-Blackfan syndrome are associated with an increased risk of MDS.

Myeloproliferative Neoplasms (MPN) are characterized by the overproduction of blood cells (red blood cells, white blood cells, and/or platelets) or collagen in the bone marrow. Often the MPN will be identified because of a blood test for another condition, as some patients are asymptomatic. Common symptoms found in the array of myeloproliferative disorders include fatigue and the enlargement of the spleen (splenomegaly).

Question 480: What was the MDS/MPN subtype?

Please indicate the MDS/MPN subtype at diagnosis. For a list of MDS/MPN subtypes and their diagnostic criteria, see Appendix X MDS/MPN Substypes.

If the MDS/MPN subtype at diagnosis was “atypical chronic myeloid leukemia,” continue with question 577.

Question 481: Was the disease (MDS/MPN) therapy-related?

Agents such as radiation or systemic therapy used to treat other diseases (e.g., Hodgkin lymphoma, non-Hodgkin lymphoma, or breast cancer) can damage the marrow and lead to a secondary malignancy, such as MDS/MPN. If the diagnosis of MDS/MPN is therapy-related, select “yes.” If the diagnosis of MDS/MPN is not therapy-related, select “no.” If it is unknown if the MDS/MPN is therapy-related, select “unknown.”

Do not answer this question “yes” if the recipient developed MDS/MPN after an environmental exposure (e.g., exposure to benzene).

Question 482: Did the recipient have a predisposing condition?

A predisposing condition is a condition that contributes to the susceptibility of developing MDS/MPN. If the recipient has a documented history of a predisposing condition, select “yes” and continue with question 483. If there is no history of a predisposing condition or if predisposition is unknown, indicate “no” or “unknown” and continue with question 485.

Questions 483-484: Specify condition:

Aplastic anemia may progress to MDS and/or AML. Aplastic anemia is a broad classification referring to bone marrow failure characterized by pancytopenia and marrow hypoplasia.

Bloom syndrome is an autosomal recessive genetic disorder characterized by excessive chromosome breakage, with corresponding rearrangements. It is characterized by proportional dwarfism and sun sensitivity. The chromosomal instability seen in Bloom syndrome is generally assumed to be responsible for these individuals’ predisposition to malignancy.

Down syndrome is also a chromosomal disorder. It is characterized by an additional chromosome 21, also referred to as trisomy 21. Down syndrome patients exhibit a particular set of facial characteristics, growth deficiency, and cognitive impairment. Although Down syndrome patients have a reduced risk of developing many common malignancies, they have an increased risk of developing leukemia.

Fanconi anemia is a rare genetic blood disorder that prevents the body from producing a sufficient number of new blood cells to function properly. Abnormal blood cells may also be produced. These patients are short in stature, exhibit skeletal anomalies, and have an increased risk of developing solid tumors and leukemias.

If the recipient had a predisposing condition not listed above, select “other condition” and specify the condition in question 484.

Questions 485-486: WBC

Indicate whether the white blood cell (WBC) count was “known” or “unknown” at diagnosis. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 486. If “unknown,” continue with question 487.

Questions 487-488: Hemoglobin

Indicate whether the hemoglobin was “known” or “unknown” at diagnosis. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 488. If “unknown,” continue with question 490.

Question 489: Were RBCs transfused ≤ 30 days before the date of test?

> ! Currently there is an issue on the 2400 form regarding RBC transfusion dates. The question should read: “Were RBCs transfused ≤ 30 days before the date of test?”

Transfusions temporarily increase the red blood cell count. It is important to distinguish between a recipient whose body is creating these cells and a recipient who requires transfusions to support the counts.

Indicate if red blood cells were transfused less than or equal to 30 days prior to the testing reported in question 488.

Questions 490-491: Platelets

Indicate whether the platelet count was “known” or “unknown” at diagnosis. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 491. If “unknown,” continue with question 493.

Question 492: Were platelets transfused ≤ 7 days before date of test?

> ! Currently there is an issue on the 2400 form regarding platelet transfusion dates. The question should read: “Were platelets transfused ≤ 7 days before the date of test?”

Transfusions temporarily increase the platelet count. It is important to distinguish between a recipient whose body is creating the platelets and a recipient who requires transfusions to support the counts.

Indicate if platelets were transfused less than or equal to 7 days prior to the testing reported in question 491.

Questions 493-494: Neutrophils

Indicate whether the neutrophil percentage in the blood was “known” or “unknown” at diagnosis. If “known,” report the value documented on the laboratory report in question 494. If “unknown,” continue with question 495.

Questions 495-496: Blasts in bone marrow

> If the bone marrow pathology report states a range for blasts, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
> If the report indicates “sheets of blasts” or “packed marrow,” report 100%.
> If the report states > n% blasts, enter (n +1)% on the form. For example, if the laboratory report indicates > 90% blasts, report 91%.
> If the report states < n% blasts, enter (n -1)% on the form. For example, if the laboratory report indicates < 5% blasts, report 4%.

Indicate whether the percentage of blasts in the bone marrow was “known” or “unknown” at diagnosis. If “known,” report the percentage documented on the laboratory report in question 496. If “unknown,” continue with question 497.

Question 497: Were cytogenetics tested (conventional or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix R, Cytogenetic Abbreviations and Terminology.

Indicate if cytogenetic studies were obtained at diagnosis. If cytogenetic studies were obtained, select “yes” and continue with question 498.

If no cytogenetic studies were obtained or it is unknown if chromosome studies were performed, select “no” or “unknown” and continue with question 525.

Question 498: Results of test:

If cytogenetic studies identified abnormalities, indicate “abnormalities identified” and continue with question 499.

If cytogenetic studies yielded “no evaluable metaphases” or there were “no abnormalities” identified, continue with question 525.

Question 499: Specify the number of distinct cytogenetic abnormalities:

Indicate the total number of abnormalities at diagnosis.

Questions 500-524: Specify abnormalities identified at diagnosis:

Report all abnormalities identified by all methods of cytogenetic assessment at diagnosis by selecting “yes” or “no” for each question. Do not leave any response blank. If one or more abnormalities are best classified as “other abnormality,” select “yes” for question 523 and specify the abnormality in question 524.

Question 525: Did the recipient progress or transform to a different MDS/MPN subtype between diagnosis and the start of the preparative regimen?

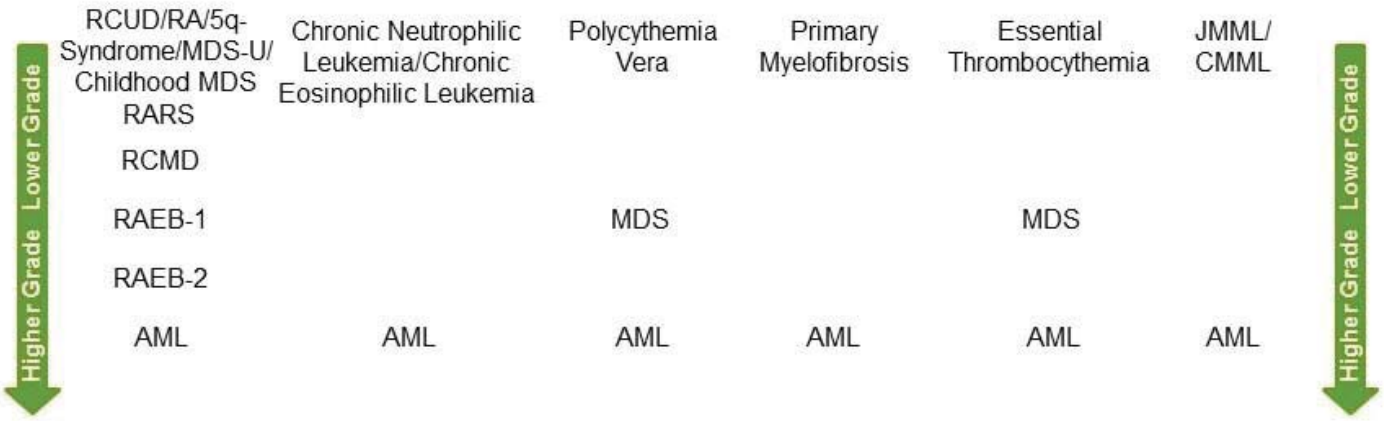
Indicate if the recipient’s disease progressed to AML or transformed into a different MDS/MPN subtype between initial diagnosis and the start of the preparative regimen. Approximately one third of MDS cases transform into AML, signifying a poorer prognosis. Progression to AML is defined by an increase in blood or bone marrow blasts equal to or greater than 20%.

MDS/MPN subtypes may also transform/progress from one into another. A progression from one subtype of MDS to another indicates that the number of cytopenias, number of blasts, and/or morphology of marrow sufficiently qualified them for a higher grade (i.e., more severe) MDS. For example, an MDS classified as RCUD at diagnosis whose blast count rises to 8% as documented on bone marrow aspirate would have progressed to RAEB-1.

Conversely, do not report a progression/transformation if the recipient’s assessments after diagnosis show that they qualify for a lower grade (i.e., less severe MDS). For example, a recipient who is diagnosed with RAEB-2, but whose assessments show that they meet the criteria for RAEB-1 as a response to treatment, would not qualify as a progression or transformation. In this example, the disease is lower grade (i.e., less severe), rather than a higher grade (i.e., more severe) so it should not be reported as a progression/transformation. See the table below for guidance in determining the severity of MDS/MPN progressions and transformations.

> ✻ Myelofibrosis that develops in patients with essential thrombocythemia (ET) or polycythemia vera (PV) is considered secondary myelofibrosis. Do not report this as a transformation; when a patient with ET or PV develops fibrosis, do not report primary myelofibrosis as the primary indication for transplant.

Grade of MDS Progression/Transformations



Indicate if the recipient's disease progressed to AML or transformed from one MDS/MPN subtype to another. If the recipient's disease did transform or progress, select "yes" and continue with question 526. If there was no documented transformation or progression, select "no" and continue with question 528.

If there was no documented transformation or progression and the disease subtype is JMML, continue to the signature line.

For a list of MDS/MPN subtypes and their diagnostic criteria, see Appendix X, MDS/MPN Subtypes.

Question 526: Specify the date of the most recent transformation:

Report the date of assessment that determined the ***most recent*** disease transformation (i.e., if there were multiple transformations, report the most recent). Report the date of the pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and laboratory evaluations.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 527: Specify the MDS/MPN subtype after transformation:

Indicate the recipient's current MDS/MPN subtype after transformation. If the recipient experienced more than one transformation after diagnosis, report the most recent subtype. Unless the recipient transformed to AML, continue with question 528.

For a list of MDS/MPN subtypes and their diagnostic criteria, see Appendix X, MDS/MPN Substypes.

If the disease transformed to AML, continue to the signature line.

Questions 528-529: WBC

Indicate whether the white blood cell (WBC) count was “known” or “unknown” at the last evaluation prior to the start of the preparative regimen. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 529. If “unknown,” continue with question 530.

Questions 530-531: Hemoglobin

Indicate whether the hemoglobin was “known” or “unknown” at the last evaluation prior to the start of the preparative regimen. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 53. If “unknown,” continue with question 533.

Question 532: Was RBCs transfused < 30 days before the date of test?

> ! Currently there is an issue on the 2400 form regarding RBC transfusion dates. The question should read: “Were RBCs transfused ≤ 30 days before the date of test?”

Transfusions temporarily increase the red blood cell count. It is important to distinguish between a recipient whose body is creating these cells and a recipient who requires transfusions to support the counts.

Indicate if red blood cells were transfused less than or equal to 30 days prior to the testing reported in question 531.

Questions 533-534: Platelets

Indicate whether the platelet count was “known” or “unknown” at the last evaluation prior to the start of the preparative regimen. If “known,” report the laboratory count and unit of measure documented on the laboratory report in question 534. If “unknown,” continue with question 536.

Question 535: Were platelets transfused < 7 days before date of test?

> ! Currently there is an issue on the 2400 form regarding platelet transfusion dates. The question should read: “Were platelets transfused ≤ 7 days before the date of test?”

Transfusions temporarily increase the platelet count. It is important to distinguish between a recipient whose body is creating the platelets and a recipient who requires transfusions to support the counts.

Indicate if platelets were transfused less than or equal to 7 days prior to the testing reported in question 534.

Questions 536-537: Neutrophils

Indicate whether the neutrophil percentage in the blood was “known” or “unknown” at the last evaluation prior to the start of the preparative regimen. If “known,” report the value documented on the laboratory report in question 537. If “unknown,” continue with question 538.

Questions 538-539: Blasts in bone marrow:

> If the bone marrow pathology report states a range for blasts, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
> If the report indicates “sheets of blasts” or “packed marrow,” report 100%.
> If the report states > n% blasts, enter (n+1)% on the form. For example, if the laboratory report indicates > 90% blasts, report 91%.
> If the report states < n% blasts, enter (n-1)% on the form. For example, if the laboratory report indicates < 5% blasts, report 4%.

Indicate whether the percentage of blasts in the bone marrow was “known” or “unknown” at the last evaluation prior to the start of the preparative regimen. If “known,” report the percentage documented on the laboratory report in question 539. If “unknown,” continue with question 540.

Question 540: Were cytogenetics tested (conventional or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix R, Cytogenetic Abbreviations and Terminology.

Indicate if cytogenetic studies were obtained at the last evaluation prior to the start of the preparative regimen. If cytogenetic studies were obtained, select “yes” and continue with question 541.

If no cytogenetic studies were obtained or it is unknown if chromosome studies were performed, select “no” or “unknown” and continue with question 568.

Question 541: Results of test:

If cytogenetic studies identified abnormalities, indicate “abnormalities identified” and continue with question 542.

If cytogenetic studies yielded “no evaluable metaphases” or there were “no abnormalities” identified, continue with question 568.

Question 542: Specify the number of distinct cytogenetic abnormalities:

Indicate the total number of abnormalities at the last evaluation prior to the start of the preparative regimen.

Questions 543-567: Specify abnormalities identified at the last evaluation prior to the start of the preparative regimen:

Report all abnormalities identified by all methods of cytogenetic assessment at the last evaluation prior to the start of the preparative regimen by selecting “yes” or “no” for each question. Do not leave any response blank. If one or more abnormalities are best classified as “other abnormality” select “yes” for question 566 and specify the abnormality in question 567.

Question 568: What was the disease status?

Indicate the disease status of MDS/MPN at the last assessment prior to the start of the preparative regimen. **See MDS/MPN Response Criteria for disease status definitions.**

> ✻ “Never Treated” is not an option choice on revision four of the Pre-TED Form. When completing revision four of this form, centers should report “No Response (NR) / Stable Disease (SD)” for recipients who have only received supportive care prior to transplant.

Question 569: Specify the cell line examined to determine HI status:

Indicate the cell line examined to determine hematologic improvement. To determine the cell line, review the Hematologic Improvement criteria found in the MDS/MPN Response Criteria section. Continue with question 572.

Question 570: Date of progression

Enter the assessment date that progression from hematologic improvement was established prior to the start of the preparative regimen. Report the date of the pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and laboratory evaluations. If extramedullary disease was detected upon radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 571: Date of relapse:

Enter the assessment date that relapse from complete remission was established prior to the start of the preparative regimen. Report the date of the pathological evaluation (e.g., bone marrow) or blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and laboratory evaluations. If extramedullary disease was detected on radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), enter the date the imaging took place.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Question 572: Date assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q573-579: Other Leukemia (OL)

CLL, or chronic lymphocytic leukemia, is characterized by ≥ 5 × 10^9/L monoclonal lymphocytes with a CLL phenotype (usually co-expressed CD5 and CD23). The term SLL, or small lymphocytic lymphoma is used for non-leukemic cases with the tissue morphology and immunophenotype of CLL.

Hairy cell leukemia is characterized by the presence of abnormal B-lymphocytes in the bone marrow, peripheral blood, and spleen.

PLL, or prolymphocytic leukemia, is a type of CLL and is characterized by increased presence of immature prolymphocytes in the bone marrow and peripheral blood.

Questions 573-574: Specify the other leukemia classification

Indicate the other leukemia disease classification at diagnosis. If the subtype is not listed, report as “other leukemia” and specify the reported disease.

Question 575: Was any 17p abnormality detected?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient’s disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence in situ hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix R, Cytogenetic Abbreviations and Terminology.

Indicate if cytogenetic studies detected any 17p abnormality at any time prior to the start of the preparative regimen.

If “yes” and the disease classification is CLL, continue with question 576. If “yes” and the disease classification is PLL, continue with question 578.

If cytogenetic studies did not detect any 17p abnormality at any time prior to the start of the preparative regimen, select “no” and continue with question 576.

Question 576: Did a histologic transformation to diffuse large B-cell lymphoma (Richter syndrome) occur at any time after CLL diagnosis?

Histologic transformation may occur after CLL diagnosis. Indicate if CLL transformed into diffuse large B-cell lymphoma (known as Richter's transformation or Richter's syndrome). If CLL transformed, select "yes" and continue with question 583. If CLL did not transform, select "no" and continue with question 578.

Question 577: What was the disease status?

Indicate the disease status for atypical CML at the last evaluation prior the start of the preparative regimen and continue with question 579.

Disease Status of Atypical CML

Primary Induction Failure (PIF)
The patient received treatment for atypical CML but never achieved complete remission at any time. PIF is not limited by the number of unsuccessful treatments; this disease status only applies to recipients who have never been in complete remission.

Complete Remission (CR)
All of the following criteria are met and maintained for four or more weeks:

- Marrow with normal maturation of all cellular components
- ≤ 5% blasts in the marrow
- No signs or symptoms of the disease
  If the timeframe between achieving CR and the start date of the HCT (i.e., day 0) is less than four weeks, and the recipient is believed to be in CR, report the status at transplantation as CR.

Important: if within four weeks following transplant the recipient's status is determined to not be CR, an Error Correction Form must be submitted to change the pre-HCT status.

Include recipients with persistent cytogenetic abnormalities who otherwise meet all the criteria of CR.

Report that the recipient is in CR at the time of transplant no matter how many courses of therapy it may have taken to achieve that CR.

The number of this complete remission can be determined by using the following guidelines:

- 1st CR: no prior relapse
- 2nd CR: one prior relapse

- 3rd or higher: two or more prior relapses

Relapse (REL)
Recurrence of disease after CR. Relapse is defined as:

- > 5% blasts in the marrow
- Extramedullary disease
- Reappearance of cytogenetic abnormalities and/or molecular markers associated with the diagnosis at levels that, as determined by a physician, represent relapse.

The number of this relapse can be determined by using the following guidelines:

- 1st relapse: one prior CR
- 2nd relapse: two prior CRs
- 3rd or higher: three or more CRs

No treatment
The recipient was diagnosed with atypical CML and never treated.

Question 578: What was the disease status?

Indicate the disease status for CLL/SLL, PLL, or hairy cell leukemia at the last evaluation prior the start of the preparative regimen and continue with question 579.

Disease Status of CLL/SLL, PLL

Never Treated
The recipient was diagnosed with CLL/SLL or PLL and never treated.

Complete Remission (CR)[1]
Requires all the following:

- No evidence of lymphadenopathy[2]
- No organomegaly
- Neutrophils > 1.5×10^9/L
- Platelets > 100×10^9/L
- Hemoglobin > 11g/dL

- Lymphocytes < 4 × 10^9/L
- Bone marrow < 30% lymphocytes
- Absence of constitutional symptoms (e.g., fatigue, fevers, night sweats)

Nodular Partial Remission (nPR)

Complete response with persistent lymphoid nodules in bone marrow.

Partial Remission (PR)

Requires all of the following:

- ≥ 50% decrease in peripheral blood lymphocyte count from pre-treatment value
- ≥ 50% reduction in lymphadenopathy if present pretreatment
- ≥ 50% reduction in liver and spleen size if enlarged pretreatment
  AND one or more of the following:
- Neutrophils ≥ 1.5 × 10^9/L or 50% above baseline
- Platelets > 100 × 10^9/L or 50% improvement over baseline
- Hemoglobin > 11.0 g/dL or 50% improvement over baseline

No Response/Stable Disease (NR/SD)

No change. Not complete response, partial response, or progressive disease.

Progression

Requires one or more of the following:

- ≥ 50% increase in the sum of the products of ≥ 2 lymph nodes (≥ 1 node must be ≥ 2 cm) or new nodes≥ 50% increase in liver or spleen size, or new hepatomegaly or splenomegaly
- ≥ 50% increase in absolute lymphocyte count to ≥ 5 × 10^9/L
- Transformation to a more aggressive histology

Relapse (untreated)

The re-appearance of disease after complete recovery. Relapse should be determined by one or more diagnostic tests.

[1] Hallek, M., Cheson, B. D., Catovsky, D., Caligaris-Cappio, F., Dighiero, G., Döhner, H., … & Kipps, T. J. (2008). Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. *Blood*, 111(12), 5446-5456.

[2] Absence of significant lymphadenopathy (e.g. lymph nodes >1.5 cm in diameter) by physical examination. In clinical trials, a CT scan of the abdomen, pelvis, and thorax is desirable if previously abnormal. Lymph nodes should not be larger than 1.5 cm in diameter.

Disease Status of Hairy Cell Leukemia[2]

Never Treated

The recipient was diagnosed with hairy cell leukemia and never treated.

Complete Remission (CR)

Disappearance of all evidence of disease.

Requires all of the following:

- Neutrophils ≥ 1.5×10^9
- Hemoglobin ≥ 12.0 g/dL
- Platelets ≥ 100×10^9/L
- Absence of hairy cells on peripheral blood smear
- No palpable lymphadenopathy or hepatosplenomegaly

*Nodular Partial Remission (nPR)**

Not applicable for hairy cell leukemia.

Partial Remission (PR)

Requires all of the following:

- ≥ 50% reduction in the absolute hairy cell count in the peripheral blood and the bone marrow
- ≥ 50% improvement of all cytopenias
- ≥ 50% reduction in abnormal lymphadenopathy or hepatosplenomegaly

No Response/Stable Disease (NR/SD)

Not applicable for hairy cell leukemia.

Progression

Not applicable for hairy cell leukemia.

Relapse (untreated)

Relapse after CR:

- Reappearance of hairy cells in the peripheral blood smear and/or bone marrow (regardless of the degree of infiltration)
- Development of peripheral blood cytopenias
- Splenomegaly

Relapse after PR

- ≥ 50% increase of residual hairy cells in the marrow
- Development of cytopenias
- Splenomegaly insufficient to qualify as PR
  OR
- Reappearance of hairy cells in the bone marrow of those patients who had been classified as partial responders based on residual splenomegaly only

[2] Saven, A., Burian, C., Koziol, J. A., & Piro, L. D. (1998). Long-term follow-up of patients with hairy cell leukemia after cladribine treatment. *Blood*, 92(6), 1918-1926.

Other leukemia:

To determine the disease status, use the criteria for the leukemia that most closely resembles the disease for which this form is being completed. For questions, contact your transplant center's CIBMTR CRC.

Question 579: Date assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. The date reported should be that of the most disease-specific assessment within the pre-transplant work-up period (approximately 30 days). Clinical and hematologic assessments include pathological evaluation (e.g., bone marrow biopsy), radiographic examination (e.g., X-ray, CT scan, MRI scan, PET scan), and laboratory assessment (e.g., CBC, peripheral blood smear), in addition to clinician evaluation and physical examination. Enter the date the sample was collected for pathological and laboratory evaluations; enter the date the imaging took place for radiographic assessments.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q580-582: Hodgkin Lyphoma

Hodgkin lymphoma (HL or Hodgkin disease) is a cancer of the immune system that is marked by the presence of a type of cell called the Reed-Sternberg cell. The two major types of Hodgkin lymphoma are classical Hodgkin lymphoma (90-95% of cases) and nodular lymphocyte-predominant Hodgkin lymphoma (5-10% of cases).

Classical Hodgkin lymphoma can be further subdivided into four histologic subtypes: nodular sclerosis (NS), mixed cellularity (MC), lymphocyte deplete (LD), and lymphocyte rich (LR). Symptoms include the painless enlargement of lymph nodes, spleen, or other immune tissue. Generalized pruritus is also common and may precede the diagnosis by months. The most common sites of involvement include cervical, supraclavicular, and mediastinal lymph nodes. Central nervous system involvement may occur in rare cases. Other symptoms include fever, weight loss, fatigue, and/or night sweats.

Hodgkin Lymphoma (**HL**) and non-Hodgkin Lymphoma (**NHL**) are WHO disease classification subtypes of lymphoma. HL and NHL can transform into other disease subtypes. NHL can transform into other NHL subtypes, or into HL subtypes, but HL will rarely transform into NHL. Additionally, HL and NHL can occur at the same time.

In order to complete the correct Disease Classification questions for a recipient who has a history of both HL and NHL, **it is important to determine which disease is active prior to the start of the preparative regimen. A physician must make this determination.**

The following two scenarios are examples of the data reporting practice for recipients with a combination of HL and NHL.

Scenario 1: A recipient is being transplanted for active NHL, but has a history of HL that is in remission at the start of the preparative regimen. Report the active NHL on the Disease Classification questions, and report HL as a prior malignancy (questions 134-154).

Scenario 2: A recipient is being transplanted for both active NHL and active HL. Report this as NHL using “Other B-cell Lymphoma” and specify in question 584. Complete the Disease Classification questions for NHL.

Question 580: Specify Hodgkin lymphoma classification

Indicate the Hodgkin lymphoma disease classification at diagnosis.

Question 581: What was the disease status?

Indicate the disease status at the last evaluation prior to the start of the preparative regimen. When determining the disease status, compare the restaging assessments immediately prior to the preparative regimen to the assessments at baseline. “Baseline” is defined as the disease at diagnosis or at relapse/ progression.

Disease Untreated
The recipient was diagnosed with lymphoma and never treated.

PIF/Partial Remission (PR1)
Never in complete remission but with stable or progressive disease upon treatment, or never in complete remission but with partial remission upon treatment.

Partial remission is ≥ 50% reduction in greatest diameter of up to six largest dominant nodes or nodal masses and no new sites. For typically PET-avid lymphoma, post-treatment PET should be positive in at least one site. For variably-PET avid lymphoma, use CT criteria.

For patients with splenic or hepatic involvement, PR is a ≥ 50% reduction in sum of the product of the diameters (SPD) of nodules (for single nodule, in greatest transverse diameter) and no increase in size of liver or spleen.

Sensitivity to Chemotherapy:
Sensitivity is measured based on **the last chemotherapy given within the six months prior to HCT.** Indicate the recipient’s sensitivity to chemotherapy using the following guidelines:

- Sensitive: ≥ 50% reduction in the bi-dimensional diameters of all disease sites with no new sites of disease (PIF sen, PR1)
- Resistant: < 50% reduction in the diameter of all disease sites or development of new disease sites (PIF res)
- Unknown (PIF unk)

Complete Remission (CR1, CR2, CR3+)
Complete disappearance of all known disease. For typically PET-avid lymphoma, a post-treatment residual mass of any size is permitted as long as it is PET negative. For variably PET-avid lymphoma, all lymph nodes and nodal masses must have regressed, as measured by CT, to < 1.5 cm (for nodes > 1.5 cm before therapy) or < 1 cm (for nodes 1.1 cm to 1.5cm before therapy).

If the patient had splenic or hepatic involvement, the spleen and/or liver should no longer be palpable and any nodules have disappeared.

If the patient had evidence of bone marrow involvement, the infiltrate must be cleared on repeat biopsy. If indeterminate by morphology, immunohistochemistry should be negative.

- CR1: first complete remission
- CR2: 2nd complete remission following relapse
- CR3: 3rd or more complete remission following relapses
  Do not include PRs when calculating the number of CRs.

Relapse (Rel)
Recurrence of disease after CR.

- 1st relapse: one prior complete remission
- 2nd relapse: two prior complete remissions
- 3rd or higher: three or more complete remissions followed by relapse.

Do not include PRs when calculating the number of relapses.

Sensitivity to Chemotherapy:
Sensitivity is measured based on the **last chemotherapy given within the six months prior to HCT.** Indicate the recipient's sensitivity to chemotherapy using the following guidelines:

- Sensitive: ≥ 50% reduction in the bi-dimensional diameters of all disease sites with no new sites of disease (REL sen)
- Resistant: < 50% reduction in the diameter of all disease sites or development of new disease sites (REL res)
- Untreated: No chemotherapy was given within the 6 months prior to the preparative regimen (REL unt)
- Unknown (REL unk)

Question 582: Date assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. Report the date imaging took place for the radiographic assessment (CT, MRI, PET, or PET/CT). Report the date the sample was collected for pathological evaluation (e.g., bone marrow biopsy). If no radiographic or

pathologic assessment was performed within one month prior to transplant, report the most recent office visit in which the physician evaluated the recipient's disease status.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q583-588: Non-Hodgkin Lymphoma

Waldenstrom Macroglobulinemia
On previous versions of the CIBMTR forms, Waldenstrom Macroglobulinemia was classified as a Plasma Cell Disorder. Per the WHO disease classifications, Waldenstrom Macroglobulinemia is now classified in the Non-Hodgkin Lymphoma section.

Non-Hodgkin lymphoma (NHL) is a large group of cancers derived from lymphocytes (white blood cells). Non-Hodgkin lymphomas can occur at any age and are often marked by enlarged lymph nodes, fever, night sweats and weight loss. There are many different types of non-Hodgkin lymphoma. These types can be divided into aggressive (fast-growing), intermediate, or indolent (slow-growing) and can develop from either B-cells or T-cells. See Table 19.

Due to the aggressive nature of Precursor T- and Precursor B-cell lymphoblastic lymphoma (or lymphoma/leukemia), the primary disease reported for recipients with these malignancies should be acute lymphoblastic leukemia (T-cell lymphoblastic leukemia/lymphoma or B-cell ALL, NOS {L1/L2}).

Lymphomas that occur after bone marrow or stem cell transplantation are usually B-cell non-Hodgkin lymphomas and are collectively known as post-transplant lymphoproliferative disorders (PTLD).

For the types of NHL, see the Types of Non-Hodgkin Lymphomas table in the Disease Specific Forms section.

Hodgkin lymphoma (**HL**) and non-Hodgkin lymphoma (**NHL**) are WHO disease classification subtypes of lymphoma. HL and NHL often transform into other disease subtypes. NHL can transform into other NHL subtypes, or into HL subtypes, but HL will rarely transform into NHL. Additionally, HL and NHL can occur at the same time.

In order to complete the correct Disease Classification questions for a recipient who has a history of both HL and NHL, **it is important to determine which disease is active prior to the start of the preparative regimen.**

The following two scenarios are examples of the data reporting practice for recipients with a combination of HL and NHL.

Scenario 1: A recipient is being transplanted for active NHL, but has a history of HL that is in remission at the start of the preparative regimen. Report the active NHL on the Disease Classification questions, and report HL as a prior malignancy (questions 134-154).

Scenario 2: A recipient is being transplanted for both active NHL and active HL. Report this as NHL using "Other B-cell Lymphoma" and specify in question 584, completing the Disease Classification questions for NHL.

Questions 583-584: Specify Non-Hodgkin lymphoma classification

Indicate the non-Hodgkin lymphoma disease classification at diagnosis. If the subtype is not listed, report as "other B-cell lymphoma" or "other T-cell/NK-cell lymphoma" and specify the reported disease.

If non-Hodgkin lymphoma transforms from one subtype to another, report the most current subtype. Report the initial diagnosis date of the first subtype in question 356.

Question 585: Is the non-Hodgkin lymphoma histology reported at diagnosis (question 583) a transformation from CLL?

In some cases, CLL may evolve to a more aggressive diffuse large B-cell lymphoma (DLBCL). This is commonly referred to as Richter's syndrome or Richter's transformation.

If the current histology is a transformation from CLL, indicate "yes," continue with question 587. Also, complete the Disease Classification questions for CLL (questions 573-579).

If the current histology is not a transformation from CLL, indicate "no" and continue with question 586.

Question 586: Is the non-Hodgkin histology reported (in question 583) a transformation from, or was it diagnosed at the same time as another lymphoma (not CLL)?

Transformation may occur when a slow-growing lymphoma with an indolent clinical history changes to a more aggressive lymphoma histologically and clinically. An example of a common transformation would include follicular lymphoma evolving to a diffuse large B-cell lymphoma (DLBCL).

If a histologic transformation occurred after or concurrently with diagnosis, indicate "yes." If a histologic transformation did not occur, indicate "no."

Question 587: What was the disease status?

Indicate the disease status at the last evaluation prior to the start of the preparative regimen. When determining the disease status, compare the restaging assessments immediately prior to the preparative

regimen to the assessments at baseline. “Baseline” is defined as the disease at diagnosis or at relapse/ progression.

Disease Untreated
The recipient was diagnosed with lymphoma and never treated.

PIF/Partial Remission (PR1)
Never in complete remission but with stable or progressive disease upon treatment, or never in complete remission but with partial remission upon treatment.

Partial remission is ≥ 50% reduction in greatest diameter of up to six largest dominant nodes or nodal masses and no new sites. For typically PET-avid lymphoma, post-treatment PET should be positive in at least one site. For variably-PET avid lymphoma, use CT criteria.

For patients with splenic or hepatic involvement, PR is a ≥ 50% reduction in sum of the product of the diameters (SPD) of nodules (for single nodule, in greatest transverse diameter) and no increase in size of liver or spleen.

Sensitivity to Chemotherapy:
Sensitivity is measured based on the **last chemotherapy given within the six months prior to HCT.** Indicate the recipient’s sensitivity to chemotherapy using the following guidelines:

- Sensitive: ≥ 50% reduction in the bi-dimensional diameters of all disease sites with no new sites of disease (PIF sen, PR1)
- Resistant: < 50% reduction in the diameter of all disease sites or development of new disease sites (PIF res)
- Unknown (PIF unk)

Complete Remission (CR1, CR2, CR3+)
Complete disappearance of all known disease. For typically PET-avid lymphoma, a post-treatment residual mass of any size is permitted as long as it is PET negative. For variably PET-avid lymphoma, all lymph nodes and nodal masses must have regressed, as measured by CT, to < 1.5 cm (for nodes > 1.5 cm before therapy) or < 1 cm (for nodes 1.1 cm to 1.5cm before therapy).

If the patient had splenic or hepatic involvement, the spleen and/or liver should no longer be palpable and any nodules disappeared.

If the patient had evidence of bone marrow involvement, the infiltrate must be cleared on repeat biopsy. If indeterminate by morphology, immunohistochemistry should be negative.

- CR1: first complete remission
- CR2: 2nd complete remission following relapse
- CR3: 3rd or more complete remission following relapses

Do not include PRs when calculating the number of CRs.

Relapse (Rel)
Recurrence of disease after CR.

- 1st relapse: one prior complete remission
- 2nd relapse: two prior complete remissions
- 3rd or higher: three or more complete remissions followed by relapse.

Do not include PRs when calculating the number of relapses.

Sensitivity to Chemotherapy:
Sensitivity is measured based on the last chemotherapy given within the six months prior to HCT. Indicate the recipient's sensitivity to chemotherapy using the following guidelines:

- Sensitive: ≥ 50% reduction in the bi-dimensional diameters of all disease sites with no new sites of disease (REL sen)
- Resistant: < 50% reduction in the diameter of all disease sites or development of new disease sites (REL res)
- Untreated: No chemotherapy was given within the 6 months prior to the preparative regimen (REL unt)
- Unknown (REL unk)

Question 588: Date assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. Report the date imaging took place for the radiographic assessment (CT, MRI, PET, or PET/CT). Report the date the sample was collected for pathological evaluation (e.g., bone marrow biopsy). If no radiographic or pathologic assessment was performed within one month prior to transplant, report the most recent office visit at which the physician evaluated the recipient's disease status.

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

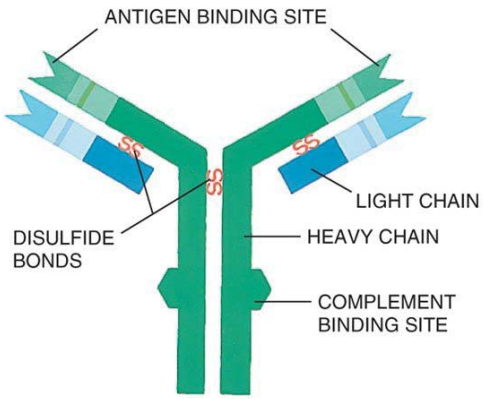
Q589-620: Multiple Myeloma/Plasma Cell Disorder (PCD)

One kind of white blood cell, the plasma cell (also called plasma B cells, plasmocytes, or effector B cells), produces proteins called antibodies or immunoglobulins (Igs) that are part of our defense system against foreign substances (called antigens). Antibodies are produced in response to such things as viruses, bacteria, and other infectious agents.

Multiple myeloma is a cancer that leads to the proliferation of malignant plasma cells (myeloma cells). Myeloma cells usually proliferate in the bone marrow. When myeloma cells grow into isolated masses in other sites, these masses are called plasmacytomas. Health problems caused by multiple myeloma can affect the bones, immune system, kidneys, and red blood cell count.

The immunoglobulins (antibodies) produced by healthy plasma cells are composed of pairs of heavy chains and light chains (see Graphic 1 below). Healthy plasma cells create many different kinds of immunoglobulins that are classified by their heavy chain type into five categories (IgG, IgA, IgM, IgD, or IgE). The light chain types are designated kappa (κ) or lambda (λ). The whole Ig molecule is then labeled IgG kappa, IgG lambda, IgA kappa, IgA lambda, etc. These protein levels can be measured in blood serum and/or urine.

Structure of an Immunoglobulin (Antibody)



Secretory Multiple Myeloma:

Healthy plasma cells make immunoglobulins (antibodies) of all types. With the proliferation of malignant plasma cells, the level of one immunoglobulin type increases in the blood and/or urine. This abnormal immunoglobulin type is called the monoclonal immunoglobulin, monoclonal protein (M-protein/M-spike/M-

component), or paraprotein. In most cases, the normal immunoglobulins are reciprocally depressed. Patients with this condition are said to have *secretory myeloma*.

Some myeloma patients make only an excess of the light chain portion of the immunoglobulin molecule (i.e., only monoclonal kappa or lambda light chains). The light chain is also called Bence Jones protein. In most patients whose myeloma cells only make light chains, this paraprotein may not be detectable in the blood, but only in the urine. These patients are said to have *light-chain-only disease*. Ninety-seven percent of patients diagnosed with multiple myeloma have a detectable paraprotein in the blood serum and/or urine.

Distribution of Monoclonal Proteins in Secretory Multiple Myeloma[12]

Monoclonal Proteins at Diagnosis	Percent
Source of monoclonal proteins	
Serum monoclonal proteins	80%
Urine monoclonal proteins	75%
Type of monoclonal proteins	
IgG	50-54%
IgA	20%
Monoclonal light chain (light-chain-only disease)	20%
IgD	2%

[1] Kyle RA, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc*. 2003;78(1):21-33.

[2] International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haem*. 2003;121(5):749-57.

Nonsecretory Multiple Myeloma:
In some myeloma patients, the malignant plasma cells do not produce an excess of the heavy chain or light chain portion of the immunoglobulin molecule; therefore, a paraprotein is not detectable in the serum or urine. These patients are said to have nonsecretory myeloma (i.e., the absence of a paraprotein on immunofixation). Immunofixation detects the specific immunoglobulins after separating the proteins into bands on an electrophoresis gel. Nonsecretory myeloma accounts for 3% of myeloma cases.

Amyloidosis:
Amyloidosis is a disease in which abnormally folded proteins build up in different tissues of the body. In the

most common amyloidosis, AL amyloidosis, the abnormally folded protein is the light chain component of an immunoglobulin. These light chains may build up in a variety of tissues, but the most common sites of build-up are the heart, kidneys, liver and nerves. According to the Amyloidosis Foundation, AL Amyloidosis is a relatively rare disorder, with 1200-3200 new cases reported each year in the United States. The disease mostly impacts men and people over 40.[3]

[3] Amyloidosis Foundation. Amyloidosis – Primary AL. 15 Apr. 2013. Accessed at: http://www.amyloidosis.org/TreatmentInformation/primaryAL.html
Accessibility verified on October 21, 2013.

Questions 589-590: Specify the multiple myeloma/plasma cell disorder (PCD) classification:

Indicate the multiple myeloma/plasma cell disorder (PCD) disease classification at diagnosis. If the subtype is not listed, report as "other plasma cell disorder" and specify the reported disease.

Multiple Myeloma (symptomatic)
Diagnostic criteria for symptomatic multiple myeloma requires all three of the following:

- Monoclonal plasma cells in marrow (≥ 10%) or biopsy-proven plasmacytoma
- M-protein in serum and/or urine. If no M-protein is detected (nonsecretory disease), then ≥ 30% plasma cells in marrow and/or biopsy-proven plasmacytoma required
- Myeloma-related organ dysfunction (≥ 1), remember the acronym CRAB
    - **C** alcium elevation (hypercalcemia, serum calcium > 10.5 mg/dL)
    - **R** enal insufficiency (serum creatinine > 2 mg/dL)
    - **A** nemia (Hemoglobin < 10 g/dL or 2 g/dL below normal)
    - **B** one Disease (lytic bone lesions and/or advanced osteoporosis)

Plasma Cell Leukemia

- Peripheral blood absolute plasma cell count of at least 2.0×10^9/L (2,000 cells/mm3)
- ≥ 20% plasma cells in the peripheral differential white blood cell count.[4]

Solitary Plasmacytoma (in absence of bone marrow findings diagnostic for multiple myeloma or plasma cell leukemia)
Extramedullary:

- No M-protein in serum and/or urine
- Extramedullary tumor of clonal plasma cells
- Normal bone marrow

- Normal skeletal survey
- No related organ or tissue impairment (end organ damage including bone lesions)

Bone Derived

- No M-protein in serum and/or urine
- Single area of bone destruction due to clonal plasma cells
- Bone marrow not consistent with multiple myeloma
- Normal skeletal survey (and MRI of spine and pelvis if done)
- No related organ or tissue impairment (no end organ damage other than solitary bone lesion)[4]

Note: if the recipient has greater than one plasmacytoma, but has not been diagnosed with another plasma cell disorder, select "other plasma cell disorder" and specify how many plasmacytomas are present and if each is bone derived or extramedullary.

Amyloidosis

Amyloidosis is the buildup of abnormally folded proteins in various tissues of the body. Affected tissues may include the kidneys, heart, liver, gastrointestinal tract, etc. In the most common type of amyloidosis, "AL amyloidosis," light chains from antibodies function as the amyloid protein, building up within organs and disrupting organ function. Serum and urine tests are useful for evaluating amyloidosis, but a tissue biopsy is the best way to diagnose the condition.

Osteosclerotic myeloma/ POEMS Syndrome

POEMS syndrome is poorly understood, but generally refers to **p** olyneuropathy, **o** rganomegaly, **e** ndocrinopathy, **M** protein, and **s** kin changes. Diagnosis may be made using the presence of the major criteria and one minor criteria below:

Major Criteria (both of the following):

- Polyneuropathy
- Monoclonal plasmaproliferative disorder

Minor Criteria (at least one of the following):

- Sclerotic bone lesions†
- Castleman disease†
- Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)
- Edema (edema, pleural effusion, or ascites)

- Endocrinopathy (adrenal, thyroid‡, pituitary, gonadal, parathyroid, pancreatic‡)
- Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)
- Papilledema

† Osteosclerotic lesion or Castleman disease is usually present.
p((. *‡ Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.*[5]

Light Chain Deposition Disease
Similar to amyloidosis, light chain deposition disease is characterized by the overproduction and deposition of light chains in organs throughout the body; however, the organ most often affected is the kidneys. Under microscopy, the pattern of deposition and the use of staining techniques help pathologists differentiate between amyloidosis and light chain deposition disease.[6]

[4] The International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma, and related disorders: a report of the international myeloma working group. *Brit J Haematol*. 2003;121(5):749-57.

[5] Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood*. 2003;101(7):2496-506.

[6] UNC Kidney Center, University of North Carolina. Light Chain Deposition Disease. 5 Apr. 2013. Accessed at: http://www.unckidneycenter.org/kidneyhealthlibrary/lightchain.html Accessibility verified on October 21, 2013

For recipients diagnosed with more than one PCD, either sequentially or concurrently, ensure that all applicable questions are completed.
If the recipient's disease classification is one of the following, continue with question 591.
1. Multiple myeloma – IgG
2. Multiple myeloma – IgA
3. Multiple myeloma – IgD
4. Multiple myeloma – IgE
5. Multiple myeloma – IgM (not Waldenstrom macroglobulinemia)
6. Multiple myeloma – light chain only

If the recipient's disease classification is the following, neither kappa nor lambda light chains will be present; therefore, continue with question 592.
7. Multiple myeloma – non-secretory

If the recipient's disease classification is one of the following, continue with question 597.
8. Plasma cell leukemia
9. Solitary plasmacytoma (no evidence of myeloma)
10. Amyloidosis
11. Osteosclerotic myeloma/POEMS syndrome
12. Light chain deposition disease

If the recipient's disease classification is the following, continue with question 590.
13. Other Plasma Cell Disorder

Question 591: Light Chain

Indicate the presence of light chains as either kappa or lambda.

Questions 592-593: What was the Durie-Salmon staging (at diagnosis)?

Indicate Durie-Salmon stage and sub-classification at diagnosis. If this is not documented in the medical record, see the table below to determine the appropriate stage and sub-classification. If "unknown," continue with question 594.

Durie-Salmon Staging System for Multiple Myeloma[7]

Stage	Criteria
I	All of the following: • Hemoglobin > 10 g/dL • Serum calcium normal (< 10.5 mg/dL) • On radiograph, normal bone structure or solitary bone plasmacytoma only • Low M-component production rate (IgG < 5 g/dL, IgA < 3 g/dL), Urinary light chain M-component on electrophoresis (< 4 g/24 hr)
II	Fitting neither stage I nor stage III
III	One or more of the following: • Hemoglobin < 8.5 g/dL • Serum calcium > 12 mg/dL • Advanced lytic bone lesions (three or more lytic lesions) • High M-component product rate (IgG > 7 g/dL, IgA > 5 g/dL), Urinary light chain M-component on electrophoresis (> 12 g/24 hr)
Sub-classification	(either A or B) A: Relatively normal renal function (serum creatinine < 2.0 mg/dL) B: Abnormal renal function (serum creatinine ≥ 2.0 mg/dL)

[7] Adapted from Durie BG, Salmon SE: A clinical staging system for multiple myeloma: Correlation of measured myeloma cell mass with presenting clinical features, response to treatment, and survival. *Cancer*. 1975;36:842-54.

Questions 594-596: Stage at Diagnosis: I.S.S.

> ! Currently there is an issue on Form 2400 regarding the ISS Staging. Stage I requires albumin greater or equal to 3.5 g/dL.

Report the recipient's lab values from diagnosis and the ISS stage of myeloma.

I.S.S. Staging System for Multiple Myeloma[8]

Stage	Description
Stage I	Serum β2-microglobulin < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
Stage II	Serum β2-microglobulin < 3.5 mg/L and serum albumin < 3.5 g/dL OR Serum β2-microglobulin 3.5 to <5.5 mg/dL irrespective of serum albumin level
Stage III	Serum β2-microglobulin ≥ 5.5 mg/L irrespective of serum albumin level

[8] Greipp, P. R., San Miguel, J., Durie, B. G., Crowley, J. J., Barlogie, B., Bladé, J., … & Westin, J. (2005). International staging system for multiple myeloma. *Journal of Clinical Oncology*, 23(15), 3412-3420.

Question 597: Were cytogenetics tested (conventional or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality that reflects the recipient's disease. Testing methods you may see include conventional chromosome analysis (karyotyping) or fluorescence *in situ* hybridization (FISH). For more information about cytogenetic testing and terminology, see Appendix R, Cytogenetic Abbreviations and Terminology.

Indicate if cytogenetic studies were obtained at any time prior to the start of the preparative regimen. If cytogenetic studies were obtained, select "yes" and continue with question 598.

If no cytogenetic studies were obtained or if it is unknown if chromosome studies were performed, select "no" or "unknown" and continue with question 619.

Question 598: Results of test:

If cytogenetic studies identified abnormalities, indicate “abnormalities identified” and continue with question 599.

If cytogenetic studies yielded “no evaluable metaphases” or there were “no abnormalities” identified, continue with question 619.

Questions 599-618: Specify abnormalities identified at any time prior to the start of the preparative regimen:

Report all abnormalities identified by all methods of cytogenetic assessment at any time prior to the start of the preparative regimen by selecting “yes” or “no” for each question. Do not leave any response blank. If one or more abnormalities are best classified as “other abnormality” select “yes” for question 617 and specify the abnormality in question 618.

Question 619: What was the disease status?

Indicate the disease status of the PCD at the last evaluation prior to the start of the preparative regimen. **See Multiple Myeloma Response Criteria for disease status definitions.**

> ! Currently there is an issue on Form 2400 regarding the number of plasma cells required for CR. CR requires less than (but not equal to) 5 % plasma cells in the bone marrow.

At any response level, if some but not all criteria are met, the disease status should be downgraded to next lower level of response.

The percentage of plasma cells in the bone marrow aspirate and/or biopsy may also be identified on a flow cytometry report. A flow cytometry report may **NOT** be used to confirm CR (e.g., < 5% plasma cells in the bone marrow).

For more information on determining how to report disease status prior to the preparative regimen, see Appendix V.

If the disease response prior to transplant is unknown, select “unknown” and continue with the signature line.

If the recipient had amyloidosis or POEMS syndrome, but no evidence of myeloma, select “not applicable” and continue with the signature line.

Example 1: A 62-year-old man is diagnosed with IgG Kappa multiple myeloma. He receives initial therapy with 6 cycles of bortezomib and lenalidomide/dexamethasone; and achieves a near complete remission (nCR). The values used to determine disease status at transplant are the values obtained at diagnosis.

Time Point	BMBX	SPEP	SIFE	UPEP	UIFE	Skeletal Survey	Treatment	Disease Status
10/31/08	27% plasma cells	3.3 g/dL	+	336 mg/24 hours	+	Negative	Bortezomib/ Lenalidomide/ Dexamethasone	Diagnosis: IgG Kappa
4/3/09	3% plasma cells							
4/17/09		Negative	+	Negative	Negative			nCR
5/13/09		Negative	+	Negative	Negative			nCR (confirmatory)
5/17/09							Autologous HCT	

Example 2: A 59-year-old woman is diagnosed with IgA Lambda multiple myeloma. She receives bortezomib and thalidomide/dexamethasone as initial treatment and achieves a CR. A few months later she has evidence of relapse. She is then treated with lenalidomide/dexamethasone and achieves a PR. The patient receives high-dose cyclophosphamide as part of an autologous stem cell harvest. The values used to determine disease status at transplant would be the values obtained at the time of relapse.

Time Point	BMBX	SPEP	SIFE	UPEP	UIFE	Skeletal Survey	Treatment	Disease Status
1/27/10		4.5 g/dL	+	Negative	Negative			
2/01/10	Aspirate=18% plasma cells; biopsy= sheets of plasma cells							Diagnosis: IgA lambda
2/05/10						Negative	Bortezomib/ Thalidomide/ Dexamethasone	
3/05/10		2.6 g/dL	+					
4/5/10		1.7 g/dL	+					

5/5/10		0.5 g/dL	+					
6/4/10		0.03 g/dL	+	Negative	Negative			
8/18/10	1% plasma cells	0.01 g/dl	+					
9/15/10		Not detected	+					
10/15/10		Not detected	Negative					CR
11/15/10		Not detected	Negative				(no treatment given)	CR (confirmatory)
12/15/11		Not detected	Negative					
1/15/11		1.9 g/dL	+	Negative	Negative			Relapse
2/15/11	7% plasma cells	2.2 g/dL	+			Negative	Lenalidomide/ Dexamethasone	Relapse (confirmatory)
3/15/11		1.4 g/dL	+					
4/15/11		0.9 g/dL	+					PR
5/15/11		0.7 g/dL	+					PR (confirmatory)
6/15/11	3% plasma cells	0.5 g/dL	+					
7/31/11							Autologous HCT	

Question 620: Date Assessed:

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. Report the date the blood/urine was collected for the laboratory evaluations (e.g., SPEP/UPEP, serum/urine immunofixation) or report the date the bone marrow was collected for pathological evaluation. A PET scan may be used if a previous PET scan had been obtained and only in limited circumstances (e.g., plasmacytomas, lytic lesions).

If the exact date is not known, use the process for reporting partial or unknown dates as described in General Instructions, Guidelines for Completing Forms.

Q621-622: Solid Tumors

Questions 621-622: Specify the solid tumor classification:

Indicate the solid tumor disease classification at the time of diagnosis. Germ cell tumors that originate in the ovary or testes should be reported as *ovarian* or *testicular*, respectively. If the subtype is not listed, report as "Other solid tumor" and specify the reported malignancy in question 622. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q623-624: Severe Aplastic Anemia

Questions 623-624: Specify the severe aplastic anemia classification:

Indicate the severe aplastic anemia disease classification at diagnosis. If the subtype is not listed, report as “other acquired cytopenic syndrome” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q625-627: Inherited Abnormalities of Erythrocyte Differentiation or Function

Questions 625-627: Specify the inherited abnormalities of erythrocyte differentiation or function classification

Indicate the inherited abnormalities of erythrocyte differentiation or function disease classification at diagnosis. If the subtype is not listed, report as “other constitutional anemia” or “other hemoglobinopathy” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q628-630: Disorders of the Immune System

Questions 628-630: Specify disorder of immune system classification:

Indicate the disorder of the immune system's disease classification at diagnosis. If the subtype is not listed, report as "other SCID" or "other immunodeficiency" and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q631-632: Inherited Abnormalities of Platelets

Questions 631-632: Specify inherited abnormalities of platelets classification:

Indicate the inherited abnormalities of platelets disease classification at diagnosis. If the subtype is not listed, report as “other inherited platelet abnormality” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q633-634: Inherited Abnormalities of Metabolism

Questions 633-634: Specify inherited abnormalities of metabolism classification:

Indicate the inherited abnormalities of metabolism disease classification at diagnosis. If the subtype is not listed, report as “inherited metabolic disorder, not otherwise specified” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q635-636: Histiocytic Disorders

Questions 635-636: Specify the histiocytic disorder classification:

Indicate the histiocytic disorder disease classification at diagnosis. If the subtype is not listed, report as “other histiocytic disorder” and specify the reported disease in question 636. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q637-644: Autoimmune Diseases

Questions 637-644: Specify autoimmune disease classification:

Indicate the autoimmune disease classification at diagnosis. If the subtype is not listed, report as “other arthritis,” “other connective tissue disease,” “other vasculitis,” “other autoimmune neurological disorder,” “other autoimmune cytopenia,” or “other autoimmune bowl disorder,” and specify the reported disease. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Q645: Other Disease

Question 645: Specify other disease:

Before using this category, check with a transplant physician to determine whether the disease can be classified as one of the listed options in the Disease Classification questions. Examples include: erythropoietic protoporphyria (EPP), and dystrophic epidermolysis bullosa (DEB).