2402: Disease Classification

The Disease Classification Form is required for all transplants, including subsequent transplants on the comprehensive report form track and cellular therapy infusions when the indication is malignant hematologic disorder, non-malignant disorder or solid tumor.

All transplant centers participating in the CIBMTR must submit a Disease Classification Form (Form 2402) for each allogeneic (related or unrelated) hematopoietic cell transplant (HCT). The Disease Classification Form 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.

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.

The Disease Classification Form may be submitted to the CIBMTR up to two weeks prior to the start of the recipient's preparative regimen.

The Disease Classification Form is designed to capture important details regarding the recipient's primary disease for which the reported HCT is being given. Key reporting areas differ depending on the disease reported (question 1), but may include disease type, subtype, transformations, cytogenetic and molecular markers, disease-specific laboratory results, staging, and disease status.

Consent Status and Baseline Forms
There has been a change to the functionality of submitting the Pre-Transplant Essential Data (2400), Pre-Transplant Essential Data Disease Classification (2402), and Pre-Cellular Therapy Essential Data (4000) forms. If a consent status has not yet been reported for a recipient, the edit form icon will appear disabled (see Figure 1 below). When the user hovers over the icon, it will display that consent has not yet been reported for that recipient (see Figure 2 below). The user should go to the Consent Tool (see Navigation to the Consent Tool) and document the recipient's consent status in order to enable the edit icon and allow for completion of the form.

Figure 1. Disabled Edit Form Icon

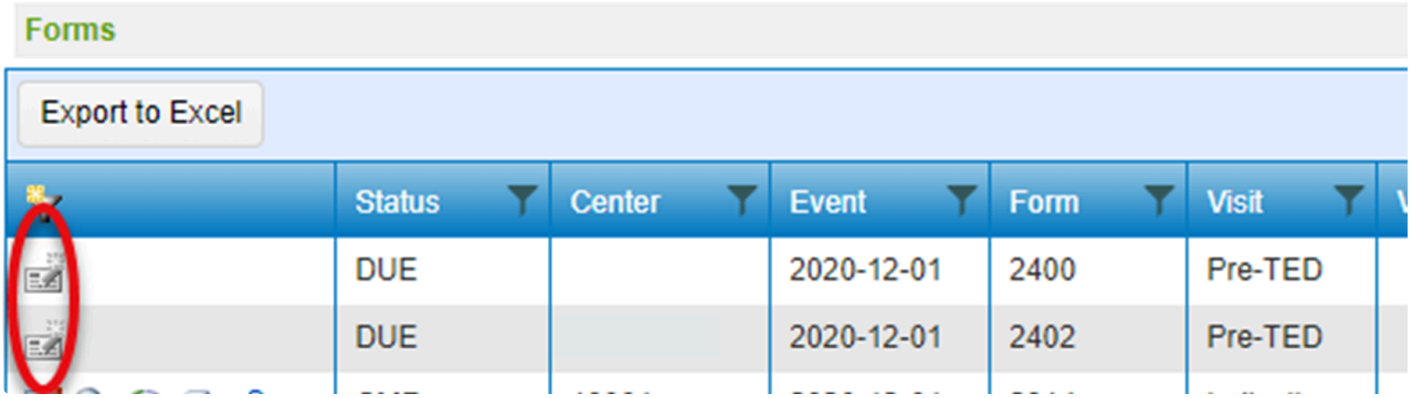
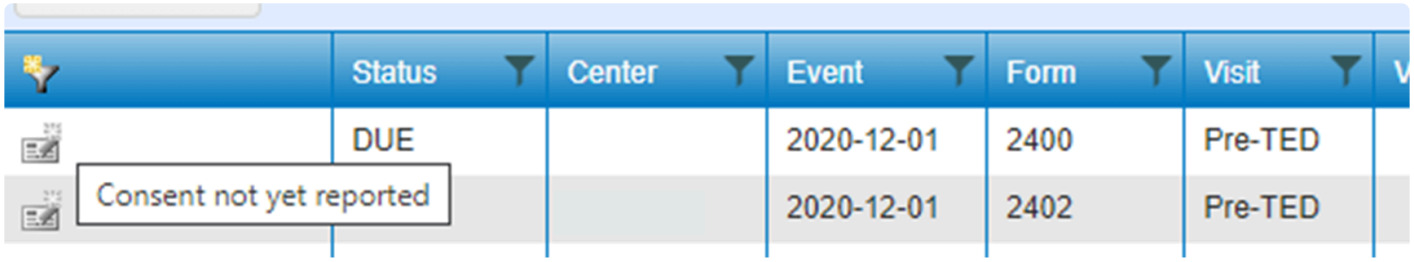


Figure 2. Hovered Text, Consent Not Yet Reported



For recipients receiving a subsequent HCT:
Transplant centers must submit a Disease Classification Form 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 (TED or CRF) 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 a subsequent Disease Classification Form in FormsNet3^{SM} until the Post-TED (Form 2450) or Post-Infusion Data Form (Form 2100) from the previous transplant has been completed.

Links to Sections of the Form:

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, review the table below or reference the retired manual section on the Retired Forms Manuals webpage.

Date	Manual Section	Add/ Remove/ Modify	Description
4/3/ 2024	2402: Disease Classification	Remove	Removed the red waring box above Q469, stating that Q469 – 501 only comes due for transfusion dependent thalassemia.
4/3/ 2024	2402: Disease Classification	Add	Instructions and example added to Q24, 51, and 78 on how to determine the FLT3-ITD allelic ratio: *The allelic ratio data field is intended to capture the ratio of the FLT3-ITD mutation. This data field does not collect the allelic frequency, the allelic frequency is used to calculate the allelic ratio. The FLT-3 ITD allelic ratio (or signal ratio) compares the number of ITD-mutated alleles to the number of wild-type (normal) alleles. If the allele frequency was assessed, the ITD-mutated allele frequency will be documented on the molecular report; however, the wild-type allele frequency will need to be calculated. To determine the wild-type allele frequency, subtract the ITD-mutated allele frequency from 1 (or 100.0). After determining the wild-type allele frequency, the allelic ratio can be assessed. To calculate the allelic ratio, divide the mutant allele frequency by the wild-type (normal) allele frequency.*
2/23/ 2024	2402: Disease Classification	Add	Instructions updated in Q408 to clarify Deauville scores should not be determined without physician / radiologist clarification: *Report whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If **Known**, report the score. Otherwise, report **Unknown**. If the PET*

			*scan result is only documented as an 'X', report this as **Unknown**. If multiple scores are documented, report the highest. If a score is not documented within the PET (or PET/CT) scan, report **Unknown** or work with the physician / radiologist to determine if a score can be reported. Do not determine Deauville scores without seeking physician / radiologist clarification.*
2/13/2024	2402: Disease Classification	Add	Instructions updated in Q408 to clarify Deauville scores should not be determined without physician / radiologist clarification: *Report whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If **Known**, report the score. Otherwise, report **Unknown**. If the PET scan result is only documented as an 'X', report this as **Unknown**. If multiple scores are documented, report the highest. If a score is not documented within the PET (or PET/CT) scan, work with the physician / radiologist to determine if a score can be reported. Do not determine Deauville scores without seeking physician / radiologist clarification.*
2/12/2024	2402: Disease Classification	Add	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis in the Laboratory Studies at Diagnosis of MDS blue box: *Report laboratory results closest to the diagnosis date and prior to the start of first treatment of the primary disease for which the HCT is being performed. If the recipient's MPN transformed, report the studies from the original diagnosis.*
2/12/2024	2402: Disease Classification	Add	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis in the Laboratory Studies at Diagnosis of MPN blue box: *Report laboratory results closest to the diagnosis date and prior to the start of first treatment of the primary disease for which the HCT is being performed. If the recipient's MPN transformed, report the studies from the original diagnosis.*
2/12/2024	2402: Disease Classification	Add	Instructions clarified when to report more than one heavy / light chain in Q415 *Indicate the heavy and / or light chain type for the recipient's disease. Select all that apply. More than one heavy and / or light chain type should only be selected for recipients diagnosed with biclonal multiple myeloma.*
10/25/2023	2402: Disease Classification	Add	Added clarification language to the blue box located below Q494: ***Laboratory studies at last evaluation*** *Complete the serum iron, TIBC, and total serum bilirubin questions based on the most recent testing prior to the start of the preparative regimen / infusion. Tests can be performed on different days.*
10/17/2023	2402: Disease Classification	Modify	Updated questions 18, 45, 72, 118, 137, 156, 229, 266, 317, 374, 452 due to the enabling of the ISCN string data field with the Summer 2023 quarterly release: ~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on*

			how to report using the ISCN functionality.
9/28/2023	2402 Q462 – 464: Severe Aplastic Anemia	Modify	Updated manual language for better clarification of severe / very severe Aplastic Anemia criteria • ***Severe / Very Severe*** *Requires ~~two of more~~ both of the following*[1]: ◦ *Bone marrow cellularity < 25% (or 25% to 50% if < 30% of residual cells are hematopoietic)* *and* ◦ *At least two of the following:* ▪ *Peripheral blood absolute neutrophil count (ANC) < 500 / µL (<0.5 x 10^9/L)* ▪ *Peripheral blood platelet count < 20,000 / µL* ▪ *Peripheral blood reticulocyte count < 20,000 / µL*
8/3/2023	2402: Disease Classification	Remove	Removed the word date from Q1 of the Hodgkin and Non-Hodgkin Lymphoma section: *If the lymphoma transformed from CLL, report the diagnosis date of the lymphoma. The CLL diagnosis ~~date~~ will be captured below.*
8/3/2023	2402: Disease Classification	Remove	Removed the word date from Q1 of the Other Leukemia section: *Ensure the Hodgkin / Non-Hodgkin Lymphoma section is completed. The CLL diagnosis ~~date~~ is captured in the Hodgkin / Non-Hodgkin Lymphoma section.*
5/2/2023	2402: Disease Classification	Add	The Follicular Lymphoma Grade Progression blue box added above Q395 and 400: ***Follicular Lymphoma Grade Progression****: Follicular lymphoma may progress to a more severe grade prior to infusion (i.e., follicular lymphoma grade I to follicular lymphoma grade II); however, progression of the grade of follicular lymphoma should not be reported as a transformation. In cases where the follicular grade progresses, report the most severe follicular lymphoma grade (i.e., the follicular grade after progression) as the histology for infusion and report* ***No****, there was not a transformation – the initial follicular grade at diagnosis will not be captured on the Disease Classification (2402) Form.*
5/1/2023	2402: Disease Classification	Add	Instructions for Q411 added on how to report lines of therapy when there was a Richter's transformation: *A single line of therapy refers to any agents administered during the same time period with the same intent (induction, consolidation, etc.). If a recipient's disease status changes resulting in a change to treatment, this should be considered a new line of therapy. Additionally, if therapy is changed because a favorable disease response was not achieved, this should be considered a new line of therapy. Do not include surgery when determining the number of lines of therapy. Report the total number of lines of therapy received since the original lymphoma diagnosis up until the start of the preparative regimen / infusion, regardless of if the recipient has received a prior infusion. If there was a transformation (lymphoma transformation or Richter's transformation), include lines of therapy given to treat the original lymphoma histology or CLL prior to*

			transformation..
4/21/2023	2402: Disease Classification	Modify	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis. These updates were made to the MDS, MPN, and PCD sections.
10/17/2022	2402: Disease Classification	Modify	Instructions updated for Q391 updated for clarification: ~~*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 the Hodgkin / Non-Hodgkin Lymphoma section. If CLL did not transform, select* ~~**No** *and report the disease status.*~~ *Always report this question as* ***No.*** *This question will be updated in future releases. If CLL transformed, the primary disease should be reported as* ***Hodgkin lymphoma*** *or* ***Non-Hodgkin's lymphoma*** *– do not report the primary disease as* ***Other leukemia.***
10/17/2022	2402: Disease Classification	Add	Red instruction box added above Q391: ***CLL with Richter's Transformation*** *If the recipient is receiving an infusion for CLL and there was a Richter's transformation to lymphoma, the primary disease for infusion should be reported as* ***Hodgkin lymphoma (150)*** *or* ***Non-Hodgkin's lymphoma (100)*** *and not* ***Other Leukemia (30)****.*
9/23/2022	2402: Disease Classification	Modify	Version 7 of the 2402: Pre-TED Disease Classification section of the Forms Instructions Manual released. Version 7 corresponds to revision 7 of the Form 2402.

Last modified: Apr 03, 2024

Q1-2: Primary Disease for HCT / Cellular Therapy

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 disease** 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 the CIBMTR Customer Service Center, 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 the CIBMTR Customer Service Center.

Subsequent HCT / Cellular Therapy for Disease Relapse:
For many diseases, the CIBMTR data collection forms capture disease assessments at multiple time points pre- and post-infusion. If the indication for this recipient's HCT / Cellular Therapy is relapsed / progressive disease and they have had a previous infusion that was reported to the CIBMTR, only disease assessments performed after the disease relapse / progression need to be reported. In this case, the disease assessments "at diagnosis" would be the disease assessments performed at the time of relapse / progression occurred (prior to the initiation of therapy). Some pre-infusion forms on the Case Report Form (CRF) track have different reporting rules, depending on if a pre-infusion CRF had been previously complete for the recipient. Carefully review the Disease-Specific CRF manuals for additional information.

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.

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

Disease Combinations	Report Primary Disease as:	Report disease diagnosis date of:	Complete multiple disease sections of the Disease Classification Form?
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

Disease Transformation	Report primary disease as:	Report disease diagnosis date of:	Complete multiple disease sections of the Disease Classification Form?
MDS or MPN to AML	AML	AML	Yes – AML and MDS or MPN
JMML to AML	AML	AML	Yes – AML and MDS (select questions only)
NHL to another NHL	Second NHL diagnosis	Second NHL diagnosis	No
HL to NHL*	NHL	NHL	No
CLL to NHL (i.e., Richter's Syndrome)	NHL	NHL	No

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.

*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 1: 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. Refer to the disease-specific section of the Disease Classification (2402) manual for guidelines when reporting the diagnosis date for each disease.

If the recipient was diagnosed prenatally (*in utero*) or was diagnosed with a **congenital** immunodeficiency, report the date of birth as the date of diagnosis.

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

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

> ! Erythropoietic protoporphyria (EPP): Historically, if the primary disease for transplant was erythropoietic protoporphyria, the primary disease for transplant was reported as “Other Disease.” However, the primary disease for transplant should be reported as “Inherited Abnormalities of Erythrocyte Differentiation or Function” in question 2 and specify the classification as “Other hemoglobinopathy” in question 359.

Question 2: What was the primary disease for which the HCT was performed?

Select the primary disease for which the recipient is receiving the HCT and continue with the appropriate disease classification questions.

Section Updates:

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

Last modified: May 01, 2023

Q3 – 103: Acute Myelogenous Leukemia

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 1: Date of diagnosis of primary disease for HCT / cellular therapy

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 AML transformed from MPS or MPN, report the diagnosis date of the AML. The MPS or MPN diagnosis date will be captured in the MDS or MPN sections below.

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

Question 3: Specify the AML classification

Indicate the disease classification at diagnosis

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 4: 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 of this form. 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 5: Is the 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 6: 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**. If there is no history of a predisposing condition or if predisposition is unknown, indicate **No** or **Unknown**, respectively.

Question 7 – 8: Specify condition

Specify the recipient's predisposing condition prior to the diagnosis of leukemia. If the recipient has a documented history of a predisposing condition but it is not listed as an option, select **Other condition** and specify the 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.

- **Dyskaratosis congenita (DKC)**, also known as Zinsser-Engman-Cole syndrome, involves progressive bone marrow failure. Patients with DKC experience skin hyperpigmentation, nail dystrophy, and oral leukoplakia (a white patch / plaque that cannot be rubbed off).

At Diagnosis, Last Evaluation, and In Between
Assessments performed at diagnosis (or at relapse), last evaluation and in between questions ask about testing performed at different time points prior to HCT. For reporting purposes, use the definitions below to determine where to report testing on the Disease Classification Form.
At Diagnosis: Any testing performed closest to (before or after) the date of diagnosis (question 1) and prior to the start of any treatment for AML.
In Between: Any pre-infusion testing which cannot be reported as part of "At Diagnosis" or "Last Evaluation."
Last Evaluation: Testing performed during the recipient's work-up for HCT or cellular therapy (generally within 30 days of the start of the preparative regimen or infusion).

Question 9: Were cytogenetics tested (karyotyping or FISH)? (at diagnosis)

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality which 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 C, Cytogenetic Assessments.

Karyotyping is performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

FISH is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA. These probes are mixed with cells from the recipient's blood or bone marrow. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

Table 3. 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 whether cytogenetic studies were performed at diagnosis or at relapse (if this form is being completed for a subsequent infusion due to relapse, see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). Do not report any testing performed after treatment for AML has started. If cytogenetic studies were obtained at diagnosis, check **Yes**. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate **No** or **Unknown**, respectively.

Question 10 – 11: Were cytogenetics tested via FISH?

If FISH studies were performed at diagnosis / relapse (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above) report **Yes** and indicate whether clonal abnormalities were detected. Do not report any testing performed after treatment for AML has started. If FISH studies were not performed at this time point or FISH sample was inadequate it is not known if performed, report **No**.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

> ! The _International System for Human Cytogenetic Nomenclature (ISCN) compatible string _question is disabled and cannot be answered at this time.

Question 12 – 15: Specify cytogenetic abnormalities (FISH)

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable.

Specify the number of abnormalities detected by FISH at diagnosis (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 16 – 17: Were cytogenetics tested via karyotyping?

If karyotyping was performed at diagnosis (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above), report **Yes** and indicate whether clonal abnormalities were detected. Do not report any testing performed after treatment for AML has started. If karyotyping was not performed at this time point or it is not known if performed, indicate **No**.

Question 18 – 21: Specify cytogenetic abnormalities (karyotyping)

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping at diagnosis / relapse (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report "see attachment" and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 22: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported in questions 9-21. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

> ✻ Questions capturing molecular marker results are intended to capture **molecular abnormalities** identified by **molecular methods**. Additional testing methods, such as FISH and chromosomal microarray, may identify molecular marker results but should **not** be reported in the molecular section(s) of the Pre-TED Disease Classification (2402) Form. Abnormalities identified by karyotyping, FISH, or chromosomal microarray should only be reported in the cytogenetic section of the Pre-TED Disease Classification (2402) Form.

Question 23: Were tests for molecular markers performed (e.g., PCR, NGS)? (at diagnosis or at relapse)

Molecular markers for disease refer to specific genetic sequences which are believed to be associated with the recipient's primary disease. Testing for these sequences is often performed using PCR based methods; however, lower sensitivity testing, including FISH, may also be used to detect molecular markers. Once a marker has been identified, these methods can be repeated to detect minimal residual disease (MRD) in the recipient's blood, marrow, or tissue. Molecular assessments include polymerase chain reaction (PCR) amplification to detect single specific disease markers; however, molecular methods are evolving and now include Sanger sequencing, and next generation sequencing (e.g., Illumina, Roche 454, Proton / PGM, SOLiD).

If testing for molecular markers was performed at diagnosis or at relapse (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above), report **Yes**.

If molecular marker testing was not performed at diagnosis or it is not known if testing was done, report **No** or **Unknown**, respectively.

Question 24 – 35: Specify results

For each molecular marker listed, report whether testing was **Positive**, **Negative**, or **Not done** at diagnosis / relapse (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If tests identified a molecular marker other than those listed, report the results in *Other molecular marker* and

specify the marker.

If multiple other molecular markers were tested, specify the results in *Other molecular marker* data field, using the following guidelines:

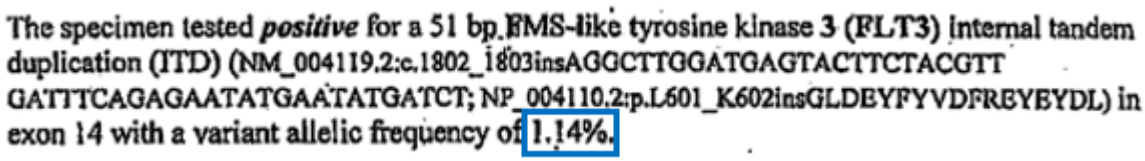
- Report one instance for all **Positive** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})
- Report one instance for any **Negative** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})

If CEBPA is reported as **Positive**, specify the CEBPA mutation. If the lab report does not specify whether the detected marker was biallelic / homozygous or monoallelic / heterozygous, confirm with the laboratory whether this information can be determined prior to reporting **Unknown**.

If FLT3-ITD is reported as **Positive**, specify the FLT3-ITD allelic ratio. If the allelic ratio is **Known**, report the value. If the lab report does not specify the allelic ratio, confirm with the laboratory whether this information can be determined prior to reporting **Unknown.**

The allelic ratio data field is intended to capture the ratio of the FLT3-ITD mutation. This data field does not collect the allelic frequency, the allelic frequency is used to calculate the allelic ratio. The FLT-3 ITD allelic ratio (or signal ratio) compares the number of ITD-mutated alleles to the number of wild-type (normal) alleles. If the allele frequency was assessed, the ITD-mutated allele frequency will be documented on the molecular report; however, the wild-type allele frequency will need to be calculated. To determine the wild-type allele frequency, subtract the ITD-mutated allele frequency from 1 (or 100.0%). After determining the wild-type allele frequency, the allelic ratio can be assessed. To calculate the allelic ratio, divide the mutant allele frequency by the wild-type (normal) allele frequency. Review the example below for more information:

Example:


The specimen tested ***positive*** for a 51 bp FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) (NM_004119.2:c.1802_1803insAGGCTTGGATGAGTACTTCTACGTT GATTTCAGAGAATATGAATATGATCT; NP_004110.2:p.L601_K602insGLDEYFYVDFREYEYDL) in exon 14 with a variant allelic frequency of 1.14%.

- ITD variant allele frequency: 1.14% (0.0114)
  - As documented in the molecular report
- Wild-type allele frequency: 98.86% (0.9886)
  - Determined by subtraction 1.14% from 100.0%
- FLT3-ITD allelic ratio: 0.0114 / 0.9886 = 0.0115

Report the FLT3-ITD allelic ratio as 0.0115

Table 4. 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.

[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 36: Were cytogenetics tested (karyotyping or FISH)? (between diagnosis and last evaluation)

Indicate whether cytogenetic studies were performed between diagnosis and the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If cytogenetic studies were obtained during this time, check **Yes**. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate **No** or **Unknown**,

respectively.

Question 37 – 38: Were cytogenetics tested via FISH?

If FISH studies were performed between diagnosis and the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above), report **Yes** and indicate whether clonal abnormalities were detected. If multiple FISH assessments were performed, report **Abnormalities Identified** if any testing showed clonal abnormalities during this period. If FISH studies were not performed during this period, FISH samples were inadequate, or is unknown if performed, report **No**.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Question 39 – 42: Specify cytogenetic abnormalities (FISH) identified between diagnosis or relapse and last evaluation

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable.

Report the number of abnormalities detected by FISH between diagnosis and the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If FISH studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities, select all clonal abnormalities detected during this period. This includes all clonal abnormalities detected any FISH assessment performed during this period.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 43 – 44: Were cytogenetics tested via karyotyping?

If karyotyping was performed between diagnosis and the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above), report **Yes** and indicate whether clonal abnormalities were detected. If multiple karyotypes were performed, report **Abnormalities Identified** if any testing showed clonal abnormalities during this period. If karyotyping was performed, but there weren’t any evaluable metaphase cells, report **Not evaluable metaphases**. If karyotyping was not performed during this period, report **No**.

Question 45 – 48: Specify cytogenetic abnormalities (karyotyping) identified between diagnosis or relapse and last evaluation

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping between diagnosis and the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If karyotype studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities, select all clonal abnormalities detected during this perio. This includes all clonal abnormalities detected any karyotype performed during this period.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 49: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

> Questions capturing molecular marker results are intended to capture **molecular abnormalities** identified by **molecular methods**. Additional testing methods, such as FISH, may identify molecular marker results but should **not** be reported in the molecular section(s) of the Pre-TED Disease Classification (2402) Form. Abnormalities identified by karyotyping, FISH, or microarray should only be reported in the cytogenetic section of the Pre-TED Disease Classification (2402) Form.

Question 50: Were tests for molecular markers performed (e.g., PCR, NGS)? (between diagnosis, or at relapse and last evaluation)

Indicate whether testing for molecular markers was performed between diagnosis and the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If testing for molecular markers was performed during this time, check **Yes**. If molecular marker testing was not obtained during this period or it is not known whether testing for molecular markers was performed, indicate **No** or **Unknown**.

Question 51 – 62: Specify molecular markers identified between diagnosis or at relapse and the last evaluation

For each molecular marker listed, report whether testing was **Positive**, **Negative**, or **Not done** between diagnosis and the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If tests identified a molecular marker other than those listed, report the

results in *Other molecular marker* and specify the marker.

If multiple other molecular markers were tested, specify the results in *Other molecular marker* data field, using the following guidelines:

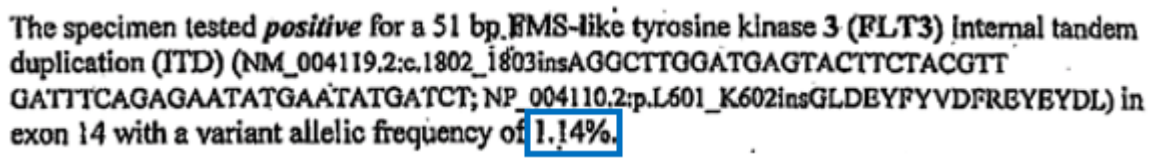
- Report one instance for all **Positive** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})
- Report one instance for any **Negative** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})

If CEBPA is reported as **Positive**, specify the CEBPA mutation. If the lab report does not specify whether the detected marker was biallelic / homozygous or monoallelic / heterozygous, confirm with the laboratory whether this information can be determined prior to reporting **Unknown**.

If FLT3-ITD is reported as **Positive**, specify the FLT3-ITD allelic ratio. If the allelic ratio is **Known**, report the value. If the lab report does not specify the allelic ratio, confirm with the laboratory whether this information can be determined prior to reporting **Unknown**.

The allelic ratio data field is intended to capture the ratio of the FLT3-ITD mutation. This data field does not collect the allelic frequency, the allelic frequency is used to calculate the allelic ratio. The FLT-3 ITD allelic ratio (or signal ratio) compares the number of ITD-mutated alleles to the number of wild-type (normal) alleles. If the allele frequency was assessed, the ITD-mutated allele frequency will be documented on the molecular report; however, the wild-type allele frequency will need to be calculated. To determine the wild-type allele frequency, subtract the ITD-mutated allele frequency from 1 (or 100.0%). After determining the wild-type allele frequency, the allelic ratio can be assessed. To calculate the allelic ratio, divide the mutant allele frequency by the wild-type (normal) allele frequency. Review the example below for more information:

Example:


The specimen tested ***positive*** for a 51 bp FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) (NM_004119.2:c.1802_1803insAGGCTTGGATGAGTACTTCTACGTT GATTTCAGAGAATATGAATATGATCT; NP_004110.2:p.L601_K602insGLDEYFYVDFREYEYDL) in exon 14 with a variant allelic frequency of 1.14%.

- ITD variant allele frequency: 1.14% (0.0114)
  - As documented in the molecular report
- Wild-type allele frequency: 98.86% (0.9886)
  - Determined by subtraction 1.14% from 100.0%
- FLT3-ITD allelic ratio: 0.0114 / 0.9886 = 0.0115

Report the FLT3-ITD allelic ratio as 0.0115

Question 63: Were cytogenetics tested (karyotyping or FISH)? (at last evaluation)

Indicate whether cytogenetic studies were performed at the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If cytogenetic studies were obtained at this time point, check **Yes**. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate **No** or **Unknown**, respectively.

Questions 64 – 65: Were cytogenetics tested via FISH?

If FISH studies were performed at the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above), report **Yes** and indicate whether clonal abnormalities were detected. If FISH studies were not performed at this time point, FISH samples were inadequate, or it is unknown if performed, report **No**.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Question 66 – 69: Specify cytogenetic abnormalities (FISH) at last evaluation

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable.

Report the number of abnormalities detected by FISH at the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” in and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 70 – 71: Were cytogenetics tested via karyotyping?

If karyotyping was performed at the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above), report **Yes** and indicate whether clonal abnormalities were detected. If karyotyping was performed, but there weren’t any evaluable metaphase cells, report **No evaluable metaphases**. If karyotyping was not performed at this time point or it is unknown is performed, indicate **No**.

Question 72 – 75: Specify cytogenetic abnormalities (karyotyping) identified at last evaluation

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping at the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify. If multiple "Other abnormalities" were detected, report "see attachment" and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 76: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

> ✻ Questions capturing molecular marker results are intended to capture **molecular abnormalities** identified by **molecular methods**. Additional testing methods, such as FISH, may identify molecular marker results but should **not** be reported in the molecular section(s) of the Pre-TED Disease Classification (2402) Form. Abnormalities identified by karyotyping, FISH, or microarray should only be reported in the cytogenetic section of the Pre-TED Disease Classification (2402) Form.

Question 77: Were tests for molecular markers performed (e.g., PCR, NGS)? (at last evaluation)

If testing for molecular markers was performed at the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above), report **Yes**. If molecular marker testing was not performed at this time point or it is not known if testing was done, report **No** or **Unknown**, respectively.

Question 78 – 89: Specify molecular marker results identified at last evaluation

For each molecular marker listed, report whether testing was **Positive**, **Negative**, or **Not done** at the last evaluation prior to infusion (see the At Diagnosis (or at relapse), Last Evaluation, and In Between blue note box above). If tests identified a molecular marker other than those listed, report the results in *Other molecular marker* and specify the marker.

If testing for other molecular markers were performed, specify the results in the *Other molecular marker* data field, using the following guidelines:

- Report one instance for all **Positive** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})
- Report one instance for any **Negative** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})

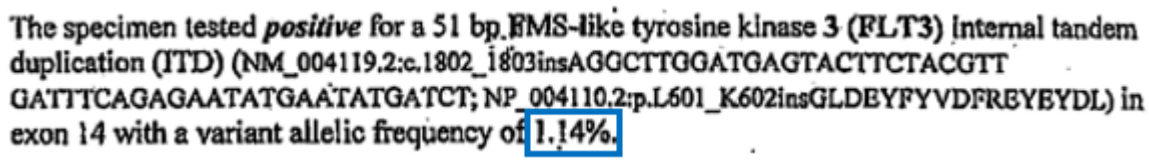
If CEBPA is reported as **Positive**, specify the CEBPA mutation. If the lab report does not specify whether

the detected marker was biallelic / homozygous or monoallelic / heterozygous, confirm with the laboratory whether this information can be determined prior to reporting **Unknown**.

If FLT3-ITD is reported as **Positive**, specify the FLT3-ITD allelic ratio. If the allelic ratio is **Known**, report the value. If the lab report does not specify the allelic ratio, confirm with the laboratory whether this information can be determined prior to reporting **Unknown**.

The allelic ratio data field is intended to capture the ratio of the FLT3-ITD mutation. This data field does not collect the allelic frequency, the allelic frequency is used to calculate the allelic ratio. The FLT-3 ITD allelic ratio (or signal ratio) compares the number of ITD-mutated alleles to the number of wild-type (normal) alleles. If the allele frequency was assessed, the ITD-mutated allele frequency will be documented on the molecular report; however, the wild-type allele frequency will need to be calculated. To determine the wild-type allele frequency, subtract the ITD-mutated allele frequency from 1 (or 100.0%). After determining the wild-type allele frequency, the allelic ratio can be assessed. To calculate the allelic ratio, divide the mutant allele frequency by the wild-type (normal) allele frequency. Review the example below for more information:

Example:


The specimen tested *positive* for a 51 bp FMS-like tyrosine kinase 3 (FLT3) internal tandem duplication (ITD) (NM_004119.2:c.1802_1803insAGGCTTGGATGAGTACTTCTACGTT GATTTCAGAGAATATGAATATGATCT; NP_004110.2:p.L601_K602insGLDEYFYVDFREYEYDL) in exon 14 with a variant allelic frequency of 1.14%.

- ITD variant allele frequency: 1.14% (0.0114)
  - As documented in the molecular report
- Wild-type allele frequency: 98.86% (0.9886)
  - Determined by subtraction 1.14% from 100.0%
- FLT3-ITD allelic ratio: 0.0114 / 0.9886 = 0.0115

Report the FLT3-ITD allelic ratio as 0.0115

Question 90: Did the recipient have central nervous system leukemia at any time prior to the start of the preparative regimen / infusion?

Central nervous system (CNS) involvement by leukemia may be detected via pathologic examination of cerebrospinal fluid or tumor tissue as well as by radiological examinations (e.g., MRI, PET/CT, MIBG, etc.). If the recipient had documented involvement of AML in the CNS, report **Yes**. If all CNS testing was negative since the time of diagnosis, report **No**. If testing for CNS involvement was not performed from the time of diagnosis to the time of HCT / cellular therapy, report **Unknown**.

Question 91: 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. Refer to the AML Response Criteria section of the Forms Instructions Manual for definitions of each response. For reporting purposes, consider complete remission with incomplete hematologic recovery (CRi) a complete

remission (CR1, CR2, or CR3+).

If the recipient did not receive any treatment for AML from the time of diagnosis to the start of the preparative regimen / infusion, report **No treatment** and continue with *Date assessed*.

If the recipient's disease status is **Primary induction failure** at the time of HCT / cellular therapy, continue with *Date assessed*.

If the recipient's disease status is **CR / CRi** at the time of HCT / cellular therapy, continue with the next question.

If the recipient's disease status is **Relapse** at the time of HCT / cellular therapy, go to *Date of most recent relapse*.

Number of Induction Cycles
The intent of this question is to capture the number of induction cycles required to achieve the *first* CR (including CRi) in the recipient's disease history, regardless of it there have been prior relapses or infusions.

Question 92: How many cycles of induction therapy were required to achieve 1st complete remission (CR)? (includes CRi)

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.

Example: A recipient diagnosed with AML, received two cycles of induction, achieved a CR and then was received one cycle of maintenance before going on to transplant. Post-transplant, the recipient relapsed, received two additional cycles of re-induction before achieving a second CR, followed by a cycle of consolidation and second transplant. The number of cycles of induction therapy to achieve the first CR should be reported as 'two.'

[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 93: Specify method(s) that was used to assess measurable residual disease status (check all that apply)

Specify the method(s) how the minimal residual status was assessed at the last evaluation, approximately 30 days prior to the start of the preparative regimen / infusion. Select all that apply.

- **FISH**: A sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA. These probes are mixed with cells from the recipient's blood or bone marrow. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

If the measurable residual disease status was assessed by FISH at the last evaluation, continue with question 94.

- **Karyotype**: A technique performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

If the measurable residual disease status was assessed by Karyotype at the last evaluation, continue with question 95.

- **Flow cytometry**: 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.

If the measurable residual disease status was assessed by Flow cytometry at the last evaluation, continue with question 96.

- **PCR**: Polymerase chain reaction (PCR) amplification is a molecular assessment used to detect single

specific disease markers. Testing for molecular markers is often performed using PCR based methods. Once a marker has been identified, this method can be repeated to detect minimal residual disease (MRD) in the recipient's blood, marrow, or tissue.

If the measurable residual disease status was assessed by PCR at the last evaluation, continue with question 100.

- **NGS**: Next-generation sequencing (NGS), also known as massive parallel sequencing is another molecular assessment which is used to determine the order of nucleotides in a genome.

If the measurable residual disease status was assessed by NGS at the last evaluation, continue with question 101.

If the minimal residual status was Not assessed at the last evaluation, continue with question 103.

Question 94: Was measurable residual disease detected by FISH?

Indicate if measurable residual disease was detected by FISH at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if measurable residual disease was detected by FISH at the last evaluation.

Question 95: Was measurable residual disease detected by karyotyping assay?

Indicate if measurable residual disease was detected by karyotype at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if minimal residual disease was detected by karyotype at the last evaluation.

> ! **Measurable Residual Disease Status**: Questions 96 – 99 are disabled and cannot be answered at this time. These questions will be updated with the next revision of the Disease Classification (2402) Form.

Questions 96 – 99: Which leukemia phenotype was used for detection? (check all that apply)

Specify which leukemia phenotype was used for detection. Select all that apply.

If the **Original leukemia immunophenotype** was used, specify the lower limit of detection, and then indicate if measurable residual disease was detected by flow cytometry at the last evaluation prior to the start of the preparative regimen / infusion.

If an **Aberrant phenotype** was used, specify the lower limit of detection, and then indicate if measurable residual disease was detected by flow cytometry at the last evaluation prior to the start of the preparative

regimen / infusion.

If the results are not clear, seek physician clarification to determine if minimal residual disease was detected by flow cytometry at the last evaluation.

Question 100: Was measurable residual disease detected by PCR?

Indicate if measurable residual disease was detected by PCR at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if measurable residual disease was detected by PCR at the last evaluation assay at the last evaluation prior to the start of the preparative regimen / infusion.

Question 101: Was measurable residual disease detected by NGS?

Indicate if measurable residual disease was detected by NGS at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if measurable residual disease was detected by NGS at the last evaluation assay at the last evaluation prior to the start of the preparative regimen / infusion.

Question 102: Date of most recent relapse

Enter the date of the most recent relapse prior to the start of the preparative regimen / infusion. 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, General Guidelines for Completing Forms.

Question 103: 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.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
18	10/17/ 2023	Modify	~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality*.	Updated due to the enabling of the ISCN string data field with the Summer 2023 quarterly release.
24	4/3/ 2024	Add	Instructions and example added on how to determine the FLT3-ITD allelic ratio: *The allelic ratio data field is intended to capture the ratio of the FLT3-ITD mutation. This data field does not collect the allelic frequency, the allelic frequency is used to calculate the allelic ratio. The FLT-3 ITD allelic ratio (or signal ratio) compares the number of ITD-mutated alleles to the number of wild-type (normal) alleles. If the allele frequency was assessed, the ITD-mutated allele frequency will be documented on the molecular report; however, the wild-type allele frequency will need to be calculated. To determine the wild-type allele frequency, subtract the ITD-mutated allele frequency from 1 (or 100.0). After determining the wild-type allele frequency, the allelic ratio can be assessed. To calculate the allelic ratio, divide the mutant allele frequency by the wild-type (normal) allele frequency.*	Added for clarification
45	10/17/ 2023	Modify	~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality*.	Updated due to the enabling of the ISCN string data field with the Summer

				2023 quarterly release.
51	4/3/ 2024	Add	Instructions and example added on how to determine the FLT3-ITD allelic ratio: *The allelic ratio data field is intended to capture the ratio of the FLT3-ITD mutation. This data field does not collect the allelic frequency, the allelic frequency is used to calculate the allelic ratio. The FLT-3 ITD allelic ratio (or signal ratio) compares the number of ITD-mutated alleles to the number of wild-type (normal) alleles. If the allele frequency was assessed, the ITD-mutated allele frequency will be documented on the molecular report; however, the wild-type allele frequency will need to be calculated. To determine the wild-type allele frequency, subtract the ITD-mutated allele frequency from 1 (or 100.0). After determining the wild-type allele frequency, the allelic ratio can be assessed. To calculate the allelic ratio, divide the mutant allele frequency by the wild-type (normal) allele frequency.*	Added for clarification
72	10/17/ 2023	Modify	~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality*.	Updated due to the enabling of the ISCN string data field with the Summer 2023 quarterly release.
78	4/3/ 2024	Add	Instructions and example added on how to determine the FLT3-ITD allelic ratio: *The allelic ratio data field is intended to capture the ratio of the FLT3-ITD mutation. This data field does not collect the allelic frequency, the allelic frequency is used to calculate the allelic ratio. The FLT-3 ITD allelic ratio (or signal ratio) compares the number of ITD-mutated alleles to the number of wild-type (normal) alleles. If the allele frequency was assessed, the ITD-mutated allele frequency will be documented on the molecular report; however, the wild-type allele frequency will need to be calculated. To determine the wild-type allele frequency, subtract the ITD-mutated allele frequency from 1 (or 100.0). After determining the wild-type allele frequency, the allelic ratio can be assessed. To calculate the allelic ratio, divide*	Added for clarification

			the mutant allele frequency by the wild-type (normal) allele frequency.	

Last modified: Apr 03, 2024

Q104 – 180: Acute Lymphoblastic Leukemia

> **Acute Lymphoblastic Lymphoma**
> 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}).

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 1: Date of diagnosis of primary disease for HCT / cellular therapy

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

Question 104: 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.

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 105: 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 98. If there is no history of a predisposing condition or if predisposition is unknown, indicate “No” or “Unknown” and continue with question 100.

Question 106 – 107: Specify condition

Indicate the recipient’s predisposing condition prior to the diagnosis of leukemia. If the recipient has a documented history of a predisposing condition but it is not listed as an option, select **Other condition** and specify the condition.

- **Aplastic anemia** is an acquired or inherited disorder of the bone marrow characterized by pancytopenia, where the body does not produce a sufficient number of new blood cells. Inherited aplastic anemias include Fanconi anemia (specified separately on this form), Shwachman-Diamond anemia, Diamond-Blackfan anemia, and dyskeratosis congenita. Acquired aplastic anemia may develop after exposures to toxins, radiation, and/or chemotherapy, or may result from an autoimmune condition such as systemic lupus erythematosus (SLE) or rheumatoid arthritis (RA). The majority of presenting signs and symptoms in aplastic anemia patients are directly related to their low blood counts and include fatigue, dizziness, shortness of breath, abnormal bleeding or bruising, and frequent infections.
- **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.

Question 108: Were tyrosine kinase inhibitors (i.e., imatinib mestylate) given for pre-HCT therapy at any time prior to the start of the preparative regimen?

Report whether the recipient received any tyrosine kinase inhibitor from the diagnosis of ALL to the start of the preparative regimen / infusion. Examples include: Imatinib mesylate is also known as Gleevec, Glivec, STI-571, or CGP57148B.

This question is optional for international centers.

At Diagnosis, Last Evaluation, and In Between
The following karyotype, FISH, and molecular questions ask about testing performed at different time points prior to HCT. For reporting purposes, use the definitions below to determine where to report testing on the Disease Classification Form.
At Diagnosis: Any testing performed closest to (before or after) the date of diagnosis (question 1) and prior to the start of any treatment for ALL.
In Between: Any testing which cannot be reported as part of either of the two above time points.
Last Evaluation: Testing performed during the recipient's work-up for HCT or cellular therapy (generally within 30 days of the start of the preparative regimen or infusion).

Question 109: Were cytogenetics tested (conventional or FISH)? (at diagnosis or at relapse)

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality which 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 C, Cytogenetic Assessments.

Karyotyping is performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

FISH is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA. These probes are mixed with cells from the recipient's blood or bone marrow. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

Table 5. Examples of ALL Cytogenetic Findings Categorized by Prognosis (Adult Precursor B-cell ALL)

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 whether cytogenetic studies were performed at diagnosis or at relapse (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). Do not report any testing performed after treatment for ALL has started. If cytogenetic studies were obtained at diagnosis, check **Yes**. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate **No** or **Unknown**, respectively.

Question 110 – 111: Were cytogenetics tested via FISH? (at diagnosis or at relapse)

If FISH studies were performed at diagnosis (see At Diagnosis or at relapse, In between, and Last Evaluation note box above), report **Yes** and indicate whether clonal abnormalities were detected. Do not report any testing performed after treatment for ALL has started. If FISH studies were not performed at this time point, FISH samples were inadequate, or it is unknown if performed, report **No**.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Question 112 – 115: Specify cytogenetic abnormalities (FISH) identified at diagnosis or at relapse

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable.

Report the number of abnormalities detected by FISH at diagnosis (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” in and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 116 – 117: Were cytogenetics tested via karyotyping? (at diagnosis or at relapse)

If karyotyping was performed at diagnosis / relapse (see At Diagnosis or at relapse, In between, and Last Evaluation note box above), report **Yes** and indicate whether clonal abnormalities were detected. Do not report any testing performed after treatment for ALL has started. If karyotyping performed, but there wasn’t any evaluable metaphase, report, **No evaluable metaphases**. If karyotyping was not performed at this time point or it is unknown, indicate **No**.

Question 118 – 121: Specify cytogenetic abnormalities (karyotyping) at diagnosis or at relapse

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping at diagnosis / relapse (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report "see attachment" and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 122: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

> ✻ Questions capturing molecular marker results are intended to capture **molecular abnormalities** identified by **molecular methods**. Additional testing methods, such as FISH or chromosomal microarray, may identify molecular marker results but should **not** be reported in the molecular section(s) of the Pre-TED Disease Classification (2402) Form. Abnormalities identified by karyotyping, FISH, or chromosomal microarray should only be reported in the cytogenetic section of the Pre-TED Disease Classification (2402) Form.

Question 123: Were tests for molecular markers performed (e.g., PCR)? (at diagnosis or at relapse)

Molecular markers for disease refer to specific genetic sequences which are believed to be associated with the recipient's primary disease. Testing for these sequences is often performed using PCR based methods; however, lower sensitivity testing, including FISH, may also be used to detect molecular markers. Once a marker has been identified, these methods can be repeated to detect minimal residual disease (MRD) in the recipient's blood, marrow, or tissue. Molecular assessments include polymerase chain reaction (PCR) amplification to detect single specific disease markers; however, molecular methods are evolving and now include Sanger sequencing, and next generation sequencing (e.g., Illumina, Roche 454, Proton / PGM, SOLiD).

If testing for molecular markers was performed at diagnosis (see At Diagnosis or at relapse, In between, and Last Evaluation note box above), report **Yes**.

If molecular marker testing was not performed at diagnosis or it is not known if testing was done, report **No** or **Unknown**, respectively.

Table 6. 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.

[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.

Questions 124 – 127: Specify molecular markers identified at diagnosis or at relapse

For each molecular marker, report whether testing was **Positive**, **Negative**, or **Not done** at diagnosis or at time of relapse (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). If tests identified a molecular marker other than those listed, report the result, and specify the marker in the allocated spaces.

If testing for other molecular markers were performed, specify the results in the *Other molecular marker data* field, using the following guidelines:

- Report one instance for all **Positive** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})
- Report one instance for any **Negative** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})

Question 128: Were cytogenetics tested (karyotyping or FISH)? (between diagnosis or relapse, and last evaluation)

Indicate whether cytogenetic studies were performed between diagnosis and the last evaluation prior to HCT / cellular therapy (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). If cytogenetic studies were obtained during this time, check **Yes**. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate **No** or **Unknown**, respectively.

Question 129 – 130: Were cytogenetics tested via FISH?

If FISH studies were performed between diagnosis and the last evaluation prior to Infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above), report **Yes** and indicate whether clonal abnormalities were detected. If multiple FISH assessments were performed, report **Abnormalities Identified** if any testing showed clonal abnormalities during this period. If FISH studies were not performed during this period, FISH samples were inadequate, or if unknown if performed, report **No**.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Question 131 – 134: Specify cytogenetic abnormalities (FISH) identified between diagnosis or at relapse and last evaluation

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable.

Report the number of abnormalities detected by FISH between diagnosis and the last evaluation prior to Infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). If FISH studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities, select all clonal abnormalities detected during this period. This includes all clonal abnormalities detected any FISH assessment performed during this period.

If a clonal abnormality is detected, but not listed as an option5, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 135 – 136: Were cytogenetics tested via karyotyping?

If karyotyping was performed between diagnosis or relapse and the last evaluation prior to Infusion (see Reporting Disease Assessments at Different Timepoints note box above), report **Yes** and indicate whether clonal abnormalities were detected. If multiple karyotypes were performed, report **Abnormalities Identified**

if any testing showed clonal abnormalities during this period. If karyotyping performed, but there wasn't any evaluable metaphase, report, **No evaluable metaphases**. If karyotyping was not performed during this period, report **No**.

Question 137 – 140: Specify cytogenetic abnormalities (karyotyping)

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping between diagnosis or relapse and the last evaluation prior to Infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). If karyotype studies showed different clonal abnormalities during this time, report the total number of clonal abnormalities detected. After indicating the number of clonal abnormalities, select all clonal abnormalities detected during this period. This includes all clonal abnormalities detected any karyotype performed during this period.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report "see attachment" and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 141: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

> ✻ Questions related to capturing molecular marker results are intended to capture **molecular abnormalities** identified by **molecular methods**. Additional testing methods, such as FISH, may identify molecular marker results but should **not** be reported in the molecular section(s) of the Pre-TED Disease Classification (2402) Form. Abnormalities identified by karyotyping, FISH, or microarray should only be reported in the cytogenetic section of the Pre-TED Disease Classification (2402) Form.

Question 142: Were tests for molecular markers performed (e.g., PCR)? (between diagnosis or relapse and last evaluation)

Indicate whether testing for molecular markers was performed between diagnosis and the last evaluation prior to Infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). If testing for molecular markers was performed during this time, check **Yes**. If molecular markers were not obtained during this period or it is not known whether testing for molecular markers was performed, indicate **No** or **Unknown**, respectively.

Question 143 – 146: Specify molecular markers identified between diagnosis or relapse and last evaluation

For each molecular marker in questions 135-136, report whether testing was “Positive,” “Negative,” or “Not done” between diagnosis and the last evaluation prior to Infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). If tests identified a molecular marker other than those listed, report the result in *Other molecular marker*, and specify the marker.

If testing for other molecular markers were performed, specify the results in the *Other molecular marker* data field, using the following guidelines

- Report one instance for all Positive other molecular markers and specify the markers (or report ‘see attachment’ and upload the report(s) using the attachment feature in FormsNet3^{SM})
- Report one instance for any **Negative** other molecular markers and specify the markers (or report ‘see attachment’ and upload the report(s) using the attachment feature in FormsNet3^{SM})

Question 147: Were cytogenetics tested (karyotyping or FISH)? (at last evaluation)

Indicate whether cytogenetic studies were performed at the last evaluation prior to infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). Do not report any testing performed after the start of the preparative regimen for ALL. If cytogenetic studies were obtained at this time point, check **Yes**. If cytogenetic studies were not obtained at this time point or it is not known whether chromosome studies were performed, indicate **No** or **Unknown**, respectively.

Question 148 – 149: Were cytogenetics tested via FISH?

If FISH studies were performed at the last evaluation prior to HCT / cellular (see At Diagnosis or at relapse, In between, and Last Evaluation note box above), report **Yes** and indicate whether clonal abnormalities were detected. If FISH studies were not performed or FISH sample was inadequate at this time point or is unknown if performed, report **No**.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Question 150 – 153: Specify cytogenetic abnormalities (FISH) identified at last evaluation

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable.

Report the number of abnormalities detected by FISH at the last evaluation prior to infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). After indicating the number of abnormalities select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” in and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 154 – 155: Were cytogenetics tested via karyotyping?

If karyotyping was performed at the last evaluation prior to infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above), report **Yes** and indicate whether clonal abnormalities were detected. If karyotyping was performed, but there weren’t any evaluable metaphase cells, report **No evaluable metaphases**. If karyotyping was not performed at this time point, indicate **No**.

Question 156 – 159: Specify cytogenetic abnormalities (karyotyping) identified at last evaluation

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping at the last evaluation prior to infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). Only consider clonal abnormalities associated with the recipient’s ALL when completing this section. After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” in and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 160: Was documentation submitted to the CIBMTR?

Indicate if a karyotyping or FISH testing report is attached to support the cytogenetic findings reported. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

> ✻ Questions capturing molecular marker results are intended to capture **molecular abnormalities** identified by **molecular methods**. Additional testing methods, such as FISH, may identify molecular marker results but should **not** be reported in the molecular section(s) of the Pre-TED Disease Classification (2402) Form. Abnormalities identified by karyotyping, FISH, or microarray should only be reported in the cytogenetic section of the Pre-TED Disease Classification (2402) Form.

Question 161: Were tests for molecular markers performed (e.g., PCR)? (at last evaluation)

If testing for molecular markers was performed at the last evaluation prior to infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above), report **Yes**. If molecular marker testing was not performed at this time point or it is not known if testing was done, report **No** or **Unknown**, respectively.

Questions 162 – 165: Specify molecular markers identified at last

For each molecular marker listed, report whether testing was **Positive**, **Negative**, or **Not done** at the last evaluation prior to infusion (see At Diagnosis or at relapse, In between, and Last Evaluation note box above). If tests identified a molecular marker other than those listed, report the result in *Other molecular marker*, and specify the marker.

If testing for other molecular markers were performed, specify the results in the *Other molecular marker* data field, using the following guidelines:

- Report one instance for all **Positive** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})
- Report one instance for any **Negative** other molecular markers and specify the markers (or report 'see attachment' and upload the report(s) using the attachment feature in FormsNet3^{SM})

Question 166: Did the recipient have central nervous system leukemia at any time prior to the start of the preparative regimen / infusion?

Central nervous system (CNS) involvement by leukemia may be detected via pathologic examination of cerebrospinal fluid or tumor tissue as well as by radiological examinations (e.g., MRI, PET/CT, MIBG, etc.). If the recipient had documented involvement of ALL in the CNS, report **Yes. If all CNS testing was negative since the time of diagnosis, report *No**. If testing for CNS involvement was not performed from the time of diagnosis to the time of HCT / cellular therapy, report **Unknown**.

Question 167: What was the disease status (based on hematological test results)?

Indicate the disease status of ALL at the last evaluation prior to the start of the preparative regimen. Refer to the ALL Response Criteria section of the Forms Instructions Manual for definitions of each response. For reporting purposes, consider complete remission with incomplete hematologic recovery (CRi) a complete remission (CR1, CR2, or CR3+).

If the recipient did not receive any treatment for ALL from the time of diagnosis to the start of the preparative regimen / infusion, report **No treatment** and continue with *Date assessed*.

If the recipient's disease status is **Primary induction failure** at the time of HCT / cellular therapy, continue with *Date assessed*.

If the recipient's disease status is **CR / CRi** at the time of HCT / cellular therapy, continue with *Date assessed*.

If the recipient's disease status is **Relapse** at the time of HCT / cellular therapy, continue with *Date assessed*.

Number of Induction Cycles

The intent of this question is to capture the number of induction cycles required to achieve the *first* CR in the recipient's disease history, regardless of it there have been prior relapses or infusions.

Question 168: 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.[1]

[1] 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.

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.

Example: A recipient diagnosed with ALL, received two cycles of induction, achieved a CR and then was received one cycle of maintenance before going on to transplant. Post-transplant, the recipient relapsed, received two additional cycles of re-induction before achieving a second CR, followed by a cycle of consolidation and second transplant. The number of cycles of induction therapy to achieve the first CR should be reported as 'two.'

Question 169: Specify method(s) that was used to assess measurable residual disease status (check all that apply)

Specify the method(s) how the minimal residual status was assessed at the last evaluation, approximately 30 days prior to the start of the preparative regimen / infusion. Select all that apply.

- **FISH**: A sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA. These probes are mixed with cells from the

recipient's blood or bone marrow. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

If the measurable residual disease status was assessed by FISH at the last evaluation, continue with question 170.

- **Karyotype**: A technique performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

If the measurable residual disease status was assessed by Karyotype at the last evaluation, continue with question 171.

- **Flow cytometry**: 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.

If the measurable residual disease status was assessed by Flow cytometry at the last evaluation, continue with question 172.

- **PCR**: Polymerase chain reaction (PCR) amplification is a molecular assessment used to detect single specific disease markers. Testing for molecular markers is often performed using PCR based methods. Once a marker has been identified, this method can be repeated to detect minimal residual disease (MRD) in the recipient's blood, marrow, or tissue.

If the measurable residual disease status was assessed by PCR at the last evaluation, continue with question 176.

- **NGS**: Next-generation sequencing (NGS), also known as massive parallel sequencing is another molecular assessment which is used to determine the order of nucleotides in a genome.

If the measurable residual disease status was assessed by NGS at the last evaluation, continue with question 177.

If the minimal residual status was Not assessed at the last evaluation, continue with question 179.

Question 170: Was measurable residual disease detected by FISH?

Indicate if measurable residual disease was detected by FISH at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if measurable residual disease was

detected by FISH at the last evaluation.

Question 171: Was measurable residual disease detected by karyotyping assay?

Indicate if measurable residual disease was detected by karyotype at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if measurable residual disease was detected by karyotype at the last evaluation.

> ! **Measurable Residual Disease Status**: Questions 172 – 174 are disabled and cannot be answered at this time. These questions will be updated with the next revision of the Disease Classification (2402) Form.

Questions 172 – 174: Which leukemia phenotype was used for detection? (check all that apply)

Specify which leukemia phenotype was used for detection. Select all that apply.

If the **Original leukemia immunophenotype** was used, specify the lower limit of detection in question 173, and then indicate if minimal residual disease was detected by flow cytometry at the last evaluation prior to the start of the preparative regimen / infusion.

If an **Aberrant phenotype** was used, specify the lower limit of detection in question 174, and then indicate if minimal residual disease was detected by flow cytometry at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if minimal residual disease was detected by flow cytometry at the last evaluation.

Question 175: Was measurable residual disease detected by flow cytometry?

Indicate if measurable residual disease was detected by flow cytometry at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if measurable residual disease was detected by flow cytometry at the last evaluation assay at the last evaluation prior to the start of the preparative regimen / infusion.

Question 176: Was measurable residual disease detected by PCR?

Indicate if measurable residual disease was detected by PCR at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if measurable residual disease was detected by PCR at the last evaluation assay at the last evaluation prior to the start of the preparative

regimen / infusion.

Question 177: Was minimal residual disease detected by NGS?

Indicate if minimal residual disease was detected by NGS at the last evaluation prior to the start of the preparative regimen / infusion.

If the results are not clear, seek physician clarification to determine if minimal residual disease was detected by NGS at the last evaluation assay at the last evaluation prior to the start of the preparative regimen / infusion.

Question 178: 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 179: 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.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
118, 137, 156	10/17/ 2023	Modify	~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International*	Updated due to the enabling of the ISCN string

			System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.	data field with the Summer 2023 quarterly release:

Last modified: Feb 02, 2024

Q180 – 183: Acute Leukemias of Ambiguous Lineage and Other Myeloid Neoplasms

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

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

Questions 180 – 181: Specify acute leukemias of ambiguous lineage and other myeloid neoplasm classification

Indicate the other acute leukemia disease classification at diagnosis. If the subtype is not listed, report as* Other acute leukemia of ambiguous lineage or myeloid neoplasm* 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 182: 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.

Table 7. Disease Status of Acute Leukemia

Disease Status	Definition
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 183: 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.

Section Updates:

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

Last modified: Sep 23, 2022

Q184 – 194: Chronic Myelogenous Leukemia

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 1: Date of diagnosis of primary disease for HCT / cellular therapy

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

Question 184: Was therapy given prior to this HCT?

If the recipient received therapy to treat CML prior to this HCT, check **Yes**. Do not report a prior HCT or cellular therapy as these are captured separately on the Pre-TED Form (Form 2400). If the recipient did **not** receive therapy to treat CML, check **No**.

Question 185 – 190: 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-α**, and **Other therapy** – specify 'cytarabine'.

Question 191: What was the disease status?

Indicate the disease status of CML at the last evaluation prior to the start of the preparative regimen (or infusion if no preparative regimen was given). Refer to the CML Response Criteria section for a description of each disease response.

If the recipient is in **Complete hematologic response (CHR)** or **Chronic phase (CP)** at the start of the preparative regimen, continue with *Specify level of response*. Otherwise, go to *Number*.

Question 192: Specify level of response

If the recipient's best response to therapy is **Complete hematologic remission (CHR)** or **Chronic phase (CP)**, specify the cytogenetic / molecular response. Refer to Table 8 for definitions of cytogenetic and

molecular responses.

Table 8. Definitions of Cytogenetic and Molecular Responses to Therapy

Response	Definition
Complete molecular remission *(most favorable)*	0% BCR / ABL transcripts detected in peripheral blood or bone marrow
Major molecular remission	> 0 – 0.1% BCR / ABL transcripts detected in peripheral blood or bone marrow
Complete cytogenetic response	0% Ph+ cells detected in bone marrow
Partial cytogenetic response	> 0 – 35% Ph+ cells in bone marrow
Minor cytogenetic response	> 35 – 65% Ph+ cells in bone marrow
Minimal cytogenetic response	> 65 – 95% Ph+ cells in bone marrow
No cytogenetic response *(least favorable)*	> 95% Ph+ cells in bone marrow.

Definitions taken from Hughes, T. P., Ross, D. M. & Melo, J. V. Handbook of chronic myeloid leukemia. (Adis, 2014).

The above responses are listed from most favorable (complete molecular remission) to least favorable (no cytogenetic response). Centers should report the most favorable response achieved. For example, if a recipient has achieved a major molecular remission by PCR testing as well as a complete cytogenetic response by karyotyping / FISH, the center should report “major molecular remission.”

Question 193: Number

Indicate the number of times the recipient has been in the disease phase reported above.

Question 194: 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.

Section Updates:

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

Last modified: Dec 21, 2023

Q195 – 274: Myelodysplastic Diseases

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

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 recipients present with symptoms related to cytopenias. Most recipients 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, Shwachman-Diamond syndrome, and Diamond-Blackfan syndrome are associated with an increased risk of MDS.

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

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's MDS progressed to from a lower grade MDS to a higher grade MDS, report the diagnosis date of the original MDS diagnosis (i.e., the lower MDS grade). The transformation date (i.e., diagnosis of the higher grade) is captured below.

If the recipient's MDS transformed to AML prior to HCT, report the diagnosis date of AML and ensure the primary disease for infusion is reported as **AML**. Ensure AML section of the Disease Classification Form is completed appropriately. The MDS diagnosis date is captured below.

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

Question 195: What was the MDS subtype at diagnosis?

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

> ! *Specify MDS-U* and *Was documentation submitted to the CIBMTR* refer to MDS, unclassifiable; if the diagnosis was other than an MDS unclassifiable continue with *Was the disease MDS therapy related?*

Questions 196 – 197: Specify Myelodysplastic syndrome, unclassifiable (MDS-U)

Specify the Myelodysplastic syndrome, unclassifiable (MDS-U) and and indicate whether documentation was submitted to the CIBMTR (e.g., pathology report).

For further instructions on how to attach documents in FormsNet3 ^{SM}, refer to the Training Guide.

Question 198: Was the disease (MDS) 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.

If the diagnosis of MDS is therapy-related, select **Yes**. If the diagnosis of MDS is not therapy-related, select **No**. If it is unknown if the MDS is therapy-related, select **Unknown**.

Do not report **Yes** if the recipient developed MDS after an environmental exposure (e.g., exposure to benzene).

Question 199: Did the recipient have a predisposing condition?

A predisposing condition contributes to the susceptibility of developing MDS. Therefore, diagnosis of the condition increases the likelihood that the recipient will develop MDS. If the recipient has a documented history of a predisposing condition, select **Yes**. If there is no history of a predisposing condition or if predisposition is unknown, indicate*No* or **Unknown**.

Questions 200 – 201: Specify condition

Specify the recipient's predisposing 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. If aplastic anemia is selected and the recipient is on the CRF track, the Aplastic Anemia Pre-HCT (2028) Form will come due.
- **DDX41-associated familial MDS** is a rare germline heterozygous mutation. DDX41 represents a class of tumor suppressor genes in myeloid neoplasms.
- **Diamond-Blackfan anemia** is a rare genetic disorder that affects the ability of the marrow from producing red blood cells. These recipients may present with anemia, recipients may also exhibit physical abnormalities such as: small head size, cleft lip, webbed neck, defects of the hands and a short stature. 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 recipients are short in stature, exhibit skeletal abnormalities, and have an increased risk of developing solid tumors, MDS, and leukemias. If Fanconi anemia is selected and the recipient is on the CRF track, the Fanconi Anemia Pre-HCT (2029) Form will come due.

- **GATA2 deficiency** is a rare genetic disorder which can cause a variety of issues including viral and bacterial infections, cytopenias, myelodysplasia, myeloid leukemias, pulmonary alveolar proteinosis and lymphedema
- **Li-Fraumeni syndrome** is a rare genetic disorder which increases the risk of developing several types of cancers, notably: breast cancer, osteosarcoma, sarcoma, brain tumors and leukemias. Li-Fraumeni syndromes are associated with mutations in the TP53 gene.
- **Paroxysmal nocturnal hemoglobinuria (PNH)** is a rare genetic disorder of the blood cells. The disease is characterized by destruction of red blood cells. blood clots and impaired bone marrow function. PNH is very closely related and often derives from aplastic anemia. If PNH is selected and the recipient is on the CRF track, the Aplastic Anemia Pre-HCT (2028) Form will come due
- **RUNX1 deficiency** was previously known as “familial platelet disorder with propensity to myeloid malignancies”. Recipients with RUNX1 deficiencies typically present with mild to moderate thrombocytopenia with normal-sized platelets, functional platelets defects leading to prolonged bleeding and an increased risk to develop myelodysplastic syndromes (MDS), acute myeloid leukemia (AML), or T-cell acute lymphoblastic leukemia (T-ALL).
- **SAMD9- or SAMD9L-associated familial MDS** are germline mutations which can result in a spectrum of multisystem disorders that carry a markedly increased risk of developing myeloid malignancies.
- **Shwachman-Diamond syndrome (SDS)** is a rare autosomal recessive disorder in which is characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities.
- **Telomere biology disorder (including dyskeratosis congenita)** are a complex set of inherited conditions defined by the presence of very short telomeres. Telomere biology disorder can be characterized by bone marrow failure and lung disease.

If the recipient had a predisposing condition not listed above, select **Other condition** and specify the condition.

A list of entities that would fall into the **Other condition** category include: ETV6-related familial thrombocytopenia, ANKRD26-related familial thrombocytopenia, SRP72-related familial aplastic anemia/ MDS, MBD4-related familial leukemia, Bloom Syndrome, Noonan Syndrome, Neurofibromatosis, Downs Syndrome, ATG2B/GSKIP duplication (chromosome 14q32.2), MECOM-associated syndrome.

Laboratory Studies at Diagnosis of MDS
Report laboratory results closest to the diagnosis date prior to the start of first treatment of the primary disease for which the HCT is being performed. If the recipient’s MDS transformed, report the studies from the original diagnosis.

Question 202: Date CBC drawn

These questions are intended to capture the laboratory studies performed at the diagnosis of MDS. All

values reported must reflect testing performed prior to the start of first treatment of the primary disease for HCT. If the recipient's MDS transformed, report the studies from the original diagnosis.

Report the date the sample was drawn

Question 203 – 204: 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.

Question 205 – 206: Neutrophils

Indicate whether the neutrophil percentage in the blood was **Known** or **Unknown** at diagnosis. If **Known**, report the neutrophil percentage documented on the laboratory report.

Questions 207 – 208: Blasts in the blood

Indicate whether the percent blasts in the peripheral blood is **Known** or **Unknown** at diagnosis. If **Known**, report the laboratory value. If the percent blasts in blood at diagnosis is not known, report **Unknown**. Note, blasts are not typically seen in the peripheral blood. If blasts are NOT reported on the differential, Known and "0%" can still be reported.

Questions 209 – 210: 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.

Question 211: Were RBCs transfused ≤ 30 days before the date the CBC was drawn?

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 date the CBC was drawn as reported above.

Questions 212 – 213: 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.

Question 214: Were platelets transfused ≤ 7 days before date the CBC was drawn?

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 date the CBC was drawn as reported above.

Questions 215 – 216: 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.

If multiple methods were used to detect the percentage of blasts in the bone marrow, the aspirate differential is the preferred method; followed by flow cytometry and IHC (immunohistochemical staining).

Question 217: Were cytogenetics tested (karyotyping or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of known chromosomal abnormalities that reflect 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 C, Cytogenetic Assessments.

If no Indicate if cytogenetic studies were obtained at diagnosis. If cytogenetic studies were obtained, select **Yes**.

If cytogenetic studies were not obtained, or it is unknown if chromosome studies were performed, select **No** or **Unknown**, respectively.

Question 218: Were cytogenetics tested via FISH?

If FISH studies were performed at diagnosis, report **Yes**.

If FISH studies were not performed at diagnosis, FISH samples were inadequate, or it is unknown if performed, report **No**. See Appendix C, Cytogenetic Assessments, for assistance interpreting FISH results.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

Question 219: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If multiple sources were used to test FISH at diagnosis, the preferred sample source is the bone marrow.

Question 220: Results of tests

If FISH assessments identified abnormalities, indicate **Abnormalities identified**.

If FISH assessments were unremarkable, indicate **No abnormalities identified**.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Questions 221 – 224: Specify cytogenetic abnormalities (FISH) at diagnosis

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string.

Report the number of abnormalities detected by FISH at diagnosis. After indicating the number of abnormalities, select all abnormalities detected. If a clonal abnormality is detected, but not listed as an option, select **Other abnormality**, and specify the abnormality.

If multiple other abnormalities were detected, report "see attachment" and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 225: Was documentation submitted to the CIBMTR?

Indicate whether documentation was submitted to the CIBMTR (e.g., pathology report, FISH report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 226: Were cytogenetics tested via karyotyping?

If karyotyping was performed at diagnosis, report **Yes**. Report Yes even if there were no evaluable metaphase cells (these results will be specified below).

If karyotyping was not performed at diagnosis or it is unknown if performed, indicate **No** and continue.

Question 227: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If multiple sources were used for karyotyping assessments at diagnosis, the preferred sample source is the bone marrow.

Question 228: Results of test

If karyotyping assessments identified abnormalities, indicate **Abnormalities identified**.

If karyotyping assessments yielded **No evaluable metaphases** or there were **No abnormalities identified**, indicate as such.

Question 229 – 232: Specify cytogenetic abnormalities (karyotyping) identified at diagnosis

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string, if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping at diagnosis. After indicating the number of abnormalities, select all abnormalities detected. If a clonal abnormality is detected, but not listed as an option, select **Other abnormality**, and specify the abnormality.

If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 233: Was documentation submitted to the CIBMTR?

Indicate whether documentation was submitted to the CIBMTR (e.g., FISH report, karyotype report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 234: Did the recipient progress or transform to a different MDS subtype or AML between diagnosis and the start of the preparative regimen / infusion?

Indicate if the recipient’s disease progressed to AML or transformed into a different MDS subtype between initial diagnosis and the start of the preparative regimen / infusion. 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 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 MDS-SLD at diagnosis whose blast count rises to 8% as documented on bone marrow aspirate would have progressed to MDS-EB-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 MDS-EB-2, but whose assessments show that they meet the criteria for MDS-EB-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 progressions and transformations.

Grade of MDS Progression/Transformations

Lower Grade	>>>>>>	>>>>>>	>>>>>>	Higher Grade
MDS-SLD / MDS-RS-SLD / MDS-RS-MLD / Childhood MDS	MDS-MLD	MDS-EB-1	MDS-EB-2	AML
JMML/CMML	—	—	—	AML

Indicate if the recipient's disease progressed to AML or transformed from one MDS subtype to another. If the recipient's disease transformed or progressed, select **Yes**. If there was no documented transformation or progression, select **No**.

Question 235: Specify the MDS subtype after transformation

Indicate the recipient's current MDS subtype after transformation. If the recipient experienced more than one transformation after diagnosis, report the most recent subtype. For a list of MDS subtypes and their diagnostic criteria, see Appendix H.

If the recipient progressed or transformed to **MDS unclassifiable**, specify the MDS-U subtype. If the disease progressed to **AML**, continue with to report the date of MDS diagnosis. If MDS progresses to AML and the recipient is on the CRF track, the Acute Myelogenous Leukemia (AML) Pre-HCT (2010) Form will also come due.

For all other progressions or transformations, continue with to specify the date of the most recent transformation.

Question 236: Specify Myelodysplastic syndrome, unclassifiable (MDS-U)

The classification of myelodysplastic syndrome, unclassifiable (MDS-U) would be based off the bone marrow biopsy pathology report and can be reported as one of the following:

- **MDS-U with 1% blood blasts**
- **MDS-U with single lineage dysplasia and pancytopenia**
- **MDS-U based on defining cytogenetic abnormality**

Specify the Myelodysplastic syndrome, unclassifiable (MDS-U) using the definitions listed.

Question 237: 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 238: Date of MDS Diagnosis

If the recipient's MDS transformed to AML prior to HCT, report the date of diagnosis of MDS. 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.

Ensure the date of diagnosis for AML has been reported as the diagnosis date, AML is reported as the

primary disease for HCT, and the AML section of the Disease Classification Form has been complete appropriately. Go to the signature line.

Question 239: Date CBC drawn

Report the date the CBC was drawn at the last evaluation prior to the start of the preparative regimen / infusion. If multiple assessments were performed, report the most recent assessment prior to the start of the preparative regimen / infusion.

Questions 240 – 241: 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 / infusion. If **Known**, report the laboratory count and unit of measure documented on the laboratory report.

Questions 242 – 243: 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 / infusion. If **Known**, report the neutrophil percentage documented on the laboratory report.

Questions 244 – 245: Blasts in the blood

Indicate whether the percent blasts in the peripheral blood is **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion. If **Known**, report the laboratory value documented on the laboratory report. If the percent blasts in blood at last evaluation is not known, report **Unknown**. Note, blasts are not typically seen in the peripheral blood. If blasts are NOT reported on the differential, Known and “0%” can still be reported.

Questions 246 – 247: Hemoglobin

Indicate whether the hemoglobin was **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion. If **Known**, report the laboratory count and unit of measure documented on the laboratory report.

Question 248: Were RBCs transfused ≤ 30 days before the date the CBC was drawn?

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 date the CBC was drawn as reported above.

Questions 249 – 250: Platelets

Indicate whether the platelet count was **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion. If **Known**, report the laboratory count and unit of measure documented on

the laboratory report.

Question 251: Were platelets transfused ≤ 7 days before the date the CBC was drawn?

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 date the CBC was drawn as reported above.

Questions 252 – 253: 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 / infusion. If **Known**, report the percentage documented on the pathology report.

If multiple assessments were performed at the last evaluation, report the most recent assessment prior to the start of the preparative regimen / infusion.

Question 254: Were cytogenetics tested (karyotyping or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of known chromosomal abnormalities that reflect 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 C, Cytogenetic Assessments.

Indicate if cytogenetic studies were obtained at the last evaluation prior to the preparative regimen / infusion. If cytogenetic studies were obtained, select **Yes**.

If no cytogenetic studies were obtained, or it is unknown if chromosome studies were performed, select **No** or **Unknown**, respectively.

Question 255: Were cytogenetics tested via FISH?

Indicate if FISH studies were performed at the last evaluation prior to the start of the preparative regimen / infusion.

If FISH studies were not performed at the last evaluation prior to the start of the preparative regimen / infusion, FISH samples were inadequate, or it is unknown if performed, report **No**. See Appendix C, Cytogenetic Assessments, for assistance interpreting FISH results.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

Question 256: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If FISH studies were performed on multiple samples at the last evaluation prior to the start of the preparative regimen / infusion, the bone marrow results are the preferred sample source to report.

Question 257: Results of tests

If FISH assessments identified abnormalities, indicate **Abnormalities identified**.

If FISH assessments were unremarkable, indicate **No abnormalities identified**.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Questions 258 – 261: Specify cytogenetic abnormalities (FISH) at last evaluation prior to the start of the preparative regimen / infusion

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string, if applicable.

Report the number of abnormalities detected by FISH at the last evaluation prior to the preparative regimen / infusion. After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 262: Was documentation submitted to the CIBMTR?

Indicate whether documentation was submitted to the CIBMTR (e.g., FISH report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 263: Were cytogenetics tested via karyotyping?

If karyotyping was performed at the last evaluation prior to the preparative regimen / infusion, report **Yes**. Report **Yes** even if there were no evaluable metaphase cells (these results will be specified below).

If karyotyping was not performed at the last evaluation prior to the start of the preparative regimen / infusion or it is unknown, indicate **No**.

Question 264: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If karyotyping studies were performed on multiple samples at the last evaluation prior to the start of the preparative regimen / infusion, the bone marrow results are the preferred sample source to report

Question 265: Results of tests

If karyotyping assessments identified abnormalities, indicate **Abnormalities identified**.

If karyotyping assessments yielded **No evaluable metaphases** or there were* No abnormalities identified*, indicate as such.

Questions 266 – 269: Specify cytogenetic abnormalities (karyotyping) at last evaluation prior to the stat of the preparative regimen / infusion

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string, if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping prior to the start of the preparative regimen / infusion. After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 270: Was documentation submitted to the CIBMTR?

Indicate whether documentation was submitted to the CIBMTR (e.g., karyotype report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

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

Question 271: What was the disease status?

Indicate the disease status of MDS at the last evaluation prior to the start of the preparative regimen / infusion.

Refer to the MDS Response Criteria section of the Forms Instructions Manual for definitions of each disease response.

Question 272: 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 listed in the MDS Response Criteria section of the Forms Instructions Manual.

If the cell lines examined to determine hematologic improvement included **Hematologic Improvement – Erythroid (HI-E)**, continue with *Specify transfusion dependence.*

If the cell lines examined to determine hematologic improvement only included **Hematologic Improvement – Platelets (HI-P)** and/or **Hematologic Improvement – Neutrophils (HI-N)**.

Question 273: Specify transfusion dependence

If the recipient's pre-transplant disease status included **Hematologic improvement – Erythroid (HI-E)**, indicate the transfusion dependence at the time of determining disease status at last evaluation prior to start of the preparative regimen / infusion.

Select **Non-transfused (NTD)** if the recipient was without RBC transfusions as supportive care for the disease within a period of 16 weeks prior to the start of the preparative regimen / infusion.

Select **Low-transfusion burden (LTB)** if the recipient had 3-7 RBC transfusions within a period of 16 weeks in at least 2 transfusion episodes with a maximum of 3 RBC transfusions in 8 weeks prior to the start of the preparative regimen / infusion.

Question 274: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen / infusion. 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.

Section Updates:

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

		Modify		
202	2/12/ 2024	Add	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis in the Laboratory Studies at Diagnosis of MDS blue box: *Report laboratory results closest to the diagnosis date and prior to the start of first treatment of the primary disease for which the HCT is being performed. If the recipient's MPN transformed, report the studies from the original diagnosis.*	Added for clarification
202	4/21/ 2023	Modify	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis.	To ensure more consistent reporting, all labs for the "at diagnosis" timepoint were clarified to reflect the values obtained closest to the date of diagnosis, prior to the start of any therapy.
229, 266	10/17/ 2023	Modify	~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality*.	Updated due to the enabling of the ISCN string data field with the Summer 2023 quarterly release:

Last modified: Feb 12, 2024

Q275 – 387: Myeloproliferative Diseases

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

Transformation to Myelofibrosis:
Recipients transplanted for post-essential thrombocythemia myelofibrosis (post-ET MF) or post-polycythemia myelofibrosis (post-PV MF) will be reported as ET or PV at diagnosis (Q275). Question: 'Did the recipient progress or transform to a different MPN subtype or AML between diagnosis and the start of the preparative regimen / infusion?' must be answered "Yes".

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 recipients are asymptomatic. Common symptoms found in the array of myeloproliferative disorders include fatigue and the enlargement of the spleen (splenomegaly).

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

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's MPN progressed to from a lower grade MPN to a higher grade MPN, report the diagnosis date of the original MPN diagnosis (i.e., the lower MPN grade). The transformation date (i.e., diagnosis of the higher grade) is captured below.

If the recipient's MPN transformed to AML prior to HCT, report diagnosis date of AML and ensure the primary disease for infusion is reported as AML. The AML section of the Disease Classification Form should be completed appropriately. The MPN diagnosis date is captured below.

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

Question 275: What was the MPN subtype at diagnosis?

Indicate the MPN subtype at diagnosis.

If the MPN subtype is **Myeloproliferative neoplasm (MPN), unclassifiable**, continue with Was

documentation submitted to the CIBMTR. If the MPN subtype is **Systemic mastocytosis**, specify the systemic mastocytosis in the next question.

Question 276: Specify systemic mastocytosis

Specify the systemic mastocytosis sub-type / variant and continue with question 262.
The diagnosis of systemic mastocytosis can be made when the major criterion and at least 1 minor criterion are present, or when >/= 3 minor criteria are present.

- Major criterion: Multifocal dense infiltrates of mast cells (>/= 15 mast cells in aggregates) detected in sections of bone marrow and/or other extracutaneous organs(s).
- Minor criteria:

1. In biopsy sections of bone marrow or other extracutaneous organs, >25% of the mast cells in the infiltrate are spindle-shaped or have atypical morphology; or >25% of all mast cells in bone marrow aspirate smears are immature or atypical.
2. Detection of an activating point mutation at codon 816 of KIT in the bone marrow, blood or another extracutaneous organ.
3. Mast cells in bone marrow, blood or another extracutaneous organ express CD25, with or without CD2, in addition to normal mast cell markers.
4. Serum total tryptase is persistently >20 ng/ml, unless there is an associated myeloid neoplasm, in which case this parameter is not valid.

The diagnostic criteria for the systemic mastocytosis sub-types/variants are as follows. Each sub-type/ variant meets the general criteria for systemic mastocytosis with additional criteria for each.

1. **Indolent systemic mastocytosis**: Low mast cell burden; no evidence of an associated hematologic neoplasm; skin lesions are almost invariably present; no “C” findings
2. **Smoldering systemic mastocytosis**: >/=2 “B” findings and no “C” findings; high mast cell burden; no evidence of an associated hematologic neoplasm; does not meet criteria for mast cell leukemia
3. **Systemic mastocytosis with an associated hematologic neoplasm**: Meets the criteria for an associated hematologic neoplasm (i.e., MDS, MPN,AML, lymphoma or another hematological neoplasm classified as a distinct entity in the WHO classification).
4. **Aggressive systemic mastocytosis**: >/=1 “C” findings; does not meet the criteria for mast cell leukemia; skin lesions are usually absent.
5. **Mast Cell leukemia**: Bone marrow biopsy shows diffuse infiltrate of atypical, immature mast cells; bone marrow aspirate smears show >/=20% mast cells. In classic cases, mast cells account for >/=10% of the peripheral blood WBC, but the aleukemic variant (in which mast cells account for <10%) is more common. Skin lesions are usually absent

“B” (burden of disease) and “C” (cytoreduction-requiring) findings in systemic mastocytosis.

“B” findings

1. BM biopsy showing >30% infiltration by MC (focal, dense aggregates) and/or serum total tryptase level >200 ng/mL
2. Signs of dysplasia or myeloproliferation, in non-MC lineage(s), but insufficient criteria for definitive diagnosis of a hematopoietic neoplasm (AHNMD), with normal or slightly abnormal blood counts.
3. Hepatomegaly without impairment of liver function, and/or palpable splenomegaly without hypersplenism, and/or lymphadenopathy on palpation or imaging.

“C” findings

1. Bone marrow dysfunction manifested by one or more cytopenia(s) (ANC <1.0 × 109/L, Hgb <10 g/dL, or platelets <100 × 109/L), but no obvious non-mast cell hematopoietic malignancy.
2. Palpable hepatomegaly with impairment of liver function, ascites and/or portal hypertension.
3. Skeletal involvement with large osteolytic lesions and/or pathological fractures.
4. Palpable splenomegaly with hypersplenism.
5. Malabsorption with weight loss due to gastrointestinal mast cell infiltrates.

Question 277: Was documentation submitted to the CIBMTR (e.g. pathology report used for diagnosis)?

Indicate whether documentation for Myeloproliferative neoplasm, unclassifiable was submitted to the CIBMTR (e.g., pathology report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Questions 278: Did the recipient have constitutional symptoms (> 10% weight loss in six months, night sweats, unexplained fever higher than 37.5°C) in six months before diagnosis?

Indicate if constitutional symptoms were present at diagnosis. Constitutional symptoms are often called “B” symptoms and include unexplained fever greater than 38°C (100.4°F), night sweats, or unexplained weight loss in the six months prior to diagnosis. Indicate “yes” if any constitutional symptoms were present at or six months prior to diagnosis.

Indicate **No** if constitutional symptoms were not present at or prior to diagnosis. Indicate **Unknown** if it is not possible to determine the presence or absence of constitutional symptoms at or six months prior to diagnosis.

Laboratory Studies at Diagnosis of MPN
Report laboratory results closest to the diagnosis date and prior to the start of first treatment of the primary disease for which the HCT is being performed. If the recipient’s MPN transformed, report the studies from the original diagnosis.

Question 279: Date CBC drawn

These questions are intended to capture the laboratory studies performed at that diagnosis of MPN. All values must reflect testing performed prior to the start of first treatment of the primary disease for HCT. If the recipient’s MPN transformed, report the studies from the original diagnosis.

Report the date the sample was collected for testing.

Questions 280 – 281: 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.

Questions 282 – 283: 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.

Questions 284 – 285: Blasts in blood

Indicate whether the percent blasts in the peripheral blood is **Known** or **Unknown** at the time of diagnosis.

If **Known**, report the laboratory value. Note, blasts are not typically found in the peripheral blood. If blasts are not noted on the differential, Known and report “0%” can still be reported.

Questions 286 – 287: Hemoglobin

Indicate whether the hemoglobin was **Known** or **Unknown** at diagnosis. If **Known**, report the laboratory value and unit of measure documented on the laboratory report.

Question 288: Was RBC transfused ≤ 30 days before the CBC sample date?

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 date reported above.

Questions 289 – 290: 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.

Question 291: Were platelets transfused ≤ 7 days before the CBC sample date?

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 date reported above.

Questions 292 – 293: 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 diagnosis. If **Known**, report the percentage documented on the laboratory report.

CALR Testing
If CALR testing was performed but the lab report does not specify the type, select **Not done** for *Not defined*.

Questions 294 – 303: Were tests for driver mutations performed?

Testing for driver mutations may be performed by different methods including next generation sequencing (NGS), polymerase chain reaction (PCR), microarray, and fluorescence in situ hybridization (FISH). If testing was performed by any / all of these methods at diagnosis, report **Yes** and report the results for the most recent test(s) prior to the start of therapy.

If testing for driver mutations were not performed / sample failed or is not known if performed, report **No** or **Unknown**, respectively.

Question 304: Was documentation submitted to the CIBMTR (e.g. pathology report used for diagnosis)?

Indicate whether documentation was submitted to the CIBMTR (e.g., pathology report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 305: Were cytogenetics tested (karyotyping or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of known chromosomal abnormalities that reflect 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 C, Cytogenetic Assessments.

Indicate if cytogenetic studies were obtained at diagnosis. If cytogenetic studies were obtained, select **Yes**.

If no cytogenetic studies were obtained, or it is unknown if chromosome studies were performed, select **No** or **Unknown**, respectively.

Question 306: Were cytogenetics tested via FISH?

Indicate if FISH studies were performed at diagnosis. If FISH studies were performed, report **Yes**.

If FISH studies were not performed at diagnosis, FISH sample was inadequate, or it is not known if performed, report **No**. See Appendix C, Cytogenetic Assessments , for assistance interpreting FISH results.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

Question 307: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If multiple sources were used to test FISH, the preferred sample source to report is the bone marrow.

Question 308: Results of tests

If FISH assessments identified abnormalities, indicate **Abnormalities identified**.

If FISH assessments were unremarkable, indicate **No abnormalities identified**.

> ! The *International System of Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Questions 309 – 312: Specify cytogenetic abnormalities (FISH) at diagnosis

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string, if applicable.

Report the number of abnormalities detected by FISH at diagnosis, then select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality**, and specify the abnormality. If multiple other abnormalities were detected, report See attachment and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 313: Was documentation submitted to the CIBMTR?

Indicate whether documentation was submitted to the CIBMTR (e.g., pathology report, FISH report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 314: Were cytogenetics tested via karyotyping?

If karyotyping was performed at diagnosis, report **Yes**. Report Yes even if there were no evaluable metaphase cells (these results will be specified below).

If karyotyping was not performed at diagnosis or it is unknown if performed, report **No**.

Question 315: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If multiple sources were used for karyotyping analyses, the preferred sample source to report is the bone marrow.

Question 316: Results of tests

If karyotyping assessments identified abnormalities, indicate **Abnormalities identified**.

If karyotyping assessments yielded No evaluable metaphases or there were **No abnormalities identified**, indicate such.

Questions 317 – 320: Specify cytogenetic abnormalities (karyotyping) identified at diagnosis

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string, if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping at diagnosis. After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality**, and specify the abnormality. If multiple other abnormalities were detected, report See attachment and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 321: Was documentation submitted to the CIBMTR?

Indicate whether documentation was submitted to the CIBMTR (e.g., karyotype report). For further instructions on how to attach documents in FormsNet3 ^{SM}, refer to the Training Guide

Question 322: Did the recipient progress or transform to a different MPN subtype or AML between diagnosis and the start of the preparative regimen / infusion?

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

MPN subtypes may also transform/progress from one into another. Indicate if the recipient's disease progressed to AML or transformed into a different MPN subtype between initial diagnosis and the start of the preparative regimen / infusion. Progression to AML is defined by an increase in blood or bone marrow blasts equal to or greater than 20%.

If the recipient's disease did transform or progress, select **Yes**. If there was no documented transformation or progression select **No**.

Question 322: Specify the MPN subtype after transformation

Indicate the recipient's current MPN subtype after transformation. If the recipient experienced more than one transformation after diagnosis, report the most recent subtype. For a list of MPN subtypes and their diagnostic criteria, see Appendix H.

If the disease **Transformed to AML**, continue with *Date of MPN diagnosis*.

For all other progressions or transformations, continue with to report the date of the most recent transformation.

Question 324: 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 325: Date of MPN Diagnosis

If the recipient's MPN transformed to AML prior to HCT, report the date of diagnosis of MPN. 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.

Ensure the date of diagnosis for AML has been reported in question 1, AML is reported as the primary disease for HCT in question 2, and the AML section of the Disease Classification Form has been completed. Go to the signature line.

Question 326: Specify transfusion dependence at the last evaluation prior to the start of the preparative regimen / infusion

Indicate the transfusion dependence for the recipient at the last evaluation prior to the start of the preparative regimen / infusion.

Select **Non-transfused (NTD)** if the recipient was without RBC transfusions as supportive care for the disease within a period of 16 weeks prior to the start of the preparative regimen / infusion.

Select **Low-transfusion burden (LTB)** if the recipient had 3-7 RBC transfusions within a period of 16 weeks in at least 2 transfusion episodes with a maximum of 3 RBC transfusions in 8 weeks prior to the start of the preparative regimen / infusion.

Select **High-transfusion burden (HTB)** if the recipient had ≥8 RBCs transfusions within a period of 16 weeks or ≥4 within 8 weeks prior to the start of the preparative regimen / infusion.

Questions 327: Did the recipient have constitutional symptoms (> 10% weight loss in six months, night sweats, unexplained fever higher than 37.5°C) in six months before the last evaluation prior to the start of the preparative regimen / infusion?

Report **Yes** if constitutional symptoms were present within six months before the last evaluation prior to the preparative regimen / infusion. Constitutional symptoms are often called “B” symptoms and include unexplained fever greater than 38°C (100.4°F), night sweats, or unexplained weight loss in the six months before the last evaluation prior to the start of the preparative regimen / infusion.

Report **No** if constitutional symptoms were not present at this timepoint.

Report **Unknown** if it is not possible to determine the presence or absence of constitutional symptoms at this timepoint.

Question 328: Did the recipient have splenomegaly at last evaluation prior to the start of the preparative regimen / infusion?

Indicate if the recipient had splenomegaly at the last evaluation. Splenomegaly is often documented during the physician’s physical assessment of the recipient and represents an abnormal finding. Splenomegaly can also be detected by imaging techniques such as ultrasonography, CT or MRI.

Indicate **Yes** if splenomegaly was present at the last evaluation prior to the start of the preparative regimen / infusion.

Indicate **No** if splenomegaly was not present at the last evaluation prior to the start of the preparative regimen / infusion.

Indicate **Unknown** if it is not possible to determine the presence or absence of splenomegaly at the last evaluation prior to the start of the preparative regimen / infusion.

Indicate **Not applicable** if the question does not apply to the recipient (e.g., prior splenectomy).

Question 329: Specify the method used to measure spleen size

Indicate the method used to measure the spleen size. If spleen size is measured using multiple methods, report the most accurate assessment. Ultrasound is the most specific, and preferred, assessment.

If the method selected is **Physical assessment**, specify the spleen size below the left coastal margin below.

If the method selected is **Ultrasound** or **CT / MRI**, specify the spleen size.

Question 330: Specify the spleen size below the left coastal margin

Indicate the size of the spleen in centimeters, measured below the left coastal margin as assessed by physical exam.

Question 331: Specify the spleen size in centimeters

Indicate the size of the spleen in centimeters, as assessed by imaging (ultrasound, CT / MRI).

Question 332: Did the recipient have hepatomegaly at last evaluation prior to the start of the preparative regimen / infusion?

Indicate if the recipient had hepatomegaly at the last evaluation prior to the start of the preparative regimen / infusion. Hepatomegaly is often documented during the physician's physical assessment of the recipient and represents an abnormal finding.

Indicate **Yes** if hepatomegaly was present at the last evaluation prior to the start of the preparative regimen / infusion.

Indicate **No** if hepatomegaly was not present at the last evaluation.

Indicate **Unknown** if it is not possible to determine the presence or absence if hepatomegaly at the last evaluation prior to the start of the preparative regimen / infusion.

Question 333: Specify the method used to measure liver size

Indicate the method used to measure the liver size. If liver size is measured using multiple methods, report the most accurate assessment. Ultrasound is the most specific, and preferred, assessment.

If the method selected is **Physical assessment**, report the liver size below the right coastal margin below.

If the method selected is **Ultrasound** or **CT / MRI**, report the liver size below.

Question 334: Specify the liver size below the right coastal margin

Indicate the size of the liver in centimeters, measured below the right coastal margin as assessed by physical exam.

Question 335: Specify the liver size in centimeters

Indicate the size of the liver in centimeters, as assessed by imaging (ultrasound, CT / MRI).

Question 336: Date CBC drawn

Report the date of the CBC was drawn at the last evaluation prior to the start of the preparative regimen / infusion. If multiple CBCs were drawn, report the most recent one prior to the start of the preparative regimen / infusion.

Questions 337 – 338: 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 infusion / infusion. If **Known**, report the laboratory count and unit of

measure documented on the laboratory report.

Questions 339 – 340: 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 / infusion. If **Known**, report the value documented on the laboratory report.

Questions 341 – 342: Blasts in the blood

Indicate whether the percent blasts in the peripheral blood is **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion.

If **Known**, report the laboratory value. Note, blasts are not typically found in the peripheral blood. If blasts are not noted on the differential, **Known** and report “0%” can still be reported.

Questions 343 – 344: Hemoglobin

Indicate whether the hemoglobin was **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion. If **Known**, report the laboratory value and unit of measure documented on the laboratory report.

Question 345: Was RBCs transfused ≤ 30 days before the CBC sample date?

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 CBC sample date reported above.

Questions 346 – 347: Platelets

Indicate whether the platelet count was **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion. If **Known**, report the laboratory count and unit of measure documented on the laboratory report.

Question 348: Were platelets transfused ≤ 7 days before 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 CBC sample date reported above.

Questions 349 – 350 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 / infusion. If **Known**, report the percentage documented on the pathology report.

Questions 351 – 360: Were tests for driver mutations performed?

Testing for driver mutations may be performed by different methods including next generation sequencing (NGS), polymerase chain reaction (PCR), microarray, and fluorescence in situ hybridization (FISH). If testing was performed by any / all of these methods at the last evaluation prior to the start of the preparative regimen / infusion, report Yes and report the results for the most recent test(s).

If testing for driver mutations were not performed / sample was inadequate or is unknown, report **No** or **Unknown**, respectively.

Question 361: Was documentation submitted to the CIBMTR (e.g. pathology report used for diagnosis)?

Indicate whether documentation was submitted to the CIBMTR (e.g., pathology report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 362: Were cytogenetics tested (karyotyping or FISH)?

Cytogenetics is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of known chromosomal abnormalities that reflect 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 C, Cytogenetic Assessments.

Indicate if cytogenetic studies were obtained at the last evaluation prior to the preparative regimen / infusion. If cytogenetic studies were obtained, select **Yes**.

If no cytogenetic studies were obtained, or it is unknown if chromosome studies were performed, select **No** or **Unknown**, respectively.

Question 363: Were cytogenetics tested via FISH?

If FISH studies were performed at the last evaluation prior to the start of the preparative regimen / infusion,

report **Yes**. If FISH studies were not performed at this time point, FISH sample was inadequate, or it is unknown if performed, report **No**. See Appendix C , Cytogenetic Assessments, for assistance interpreting FISH results.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

Question 364: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If multiple sources were used to test FISH, the preferred sample source to report is the bone marrow.

Question 365: Results of tests

If FISH assessments identified abnormalities, indicate **Abnormalities identified**.

If FISH assessments were unremarkable, indicate **No abnormalities identified**.

> ! The *International System for Human Cytogenetic Nomenclature (ISCN) compatible string* is disabled and cannot be answered at this time.

Questions 366 – 369: Specify cytogenetic abnormalities (FISH)

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string, if applicable.

Report the number of abnormalities detected by FISH at the last evaluation prior to the preparative regimen / infusion. After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality**, and specify the abnormality in the allocated space. If multiple other abnormalities were detected, report See attachment and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 370: Was documentation submitted to the CIBMTR? (e.g., FISH report)

Indicate whether documentation was submitted to the CIBMTR (e.g., pathology report, FISH report). For further instructions on how to attach documents in FormsNet3SM, refer to the Training Guide.

Question 371: Were cytogenetics tested via karyotyping?

If karyotyping was performed at the last evaluation prior to the preparative regimen / infusion, report **Yes.** Report **Yes** even if there were no evaluable metaphase cells (these results will be specified below).

If karyotyping was not performed at this time point or it is unknown, indicate **No**.

Question 372: Sample source

Indicate if the sample was from **Bone marrow** or from **Blood**. If multiple sources were used to for karyotyping analyses, the preferred sample source to report is the bone marrow.

Question 373: Results of tests

If karyotyping assessments identified abnormalities, indicate **Abnormalities identified**.

If karyotyping assessments yielded **No evaluable metaphases** or there were **No abnormalities identified**, indicate such.

Questions 374 – 377: Specify cytogenetic abnormalities (karyotyping) at last evaluation prior to the start of the preparative regimen / infusion

Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string, if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Report the number of abnormalities detected by karyotyping at the last evaluation prior to the start of the preparative regimen / infusion. After indicating the number of abnormalities, select all abnormalities detected.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report 'see attachment' and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 378: Was documentation submitted to the CIBMTR (e.g., karyotyping report)?

Indicate whether documentation was submitted to the CIBMTR (e.g., karyotype report). For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 379: What was the disease status?

Indicate the disease status of MPN at the last assessment prior to the start of the preparative regimen / infusion. **Refer to the MPN Response Criteria section of the Forms Instructions Manual for definitions of each disease response**.

If the disease status is **Clinical Improvement (CI)**, continue with *Was an anemia response achieved*.

If the disease status is **Not Assessed**, continue with *Specify the cytogenetic response*.

For all other disease statuses, go to *Date assessed*.

Question 380: Was an anemia response achieved?

Specify if an anemia response has been achieved at the last evaluation prior to the preparative regimen /

infusion.

An anemia response is characterized by a ≥ 20 g/L (or > 2.0 g/dL) increase in hemoglobin level (for transfusion-independent recipients

Question 381: Was a spleen response achieved?

If a spleen response does not apply to the recipient (e.g. prior splenectomy), this question will be disabled and should not be answered.

Specify if a spleen response has been achieved at the last evaluation prior to the preparative regimen / infusion.

A spleen response is achieved when a baseline splenomegaly that is palpable at 5 – 10 cm below the left costal margin (LCM) becomes not palpable or baseline splenomegaly that is palpable at > 10 cm below the LCM, decreases by ≥ 50%.

A baseline splenomegaly that is palpable at < 5 cm, below the LCM, is not eligible for spleen response.

A spleen response can be documented by a physician but should be confirmed by MRI / computed tomography showing ≥ 35% spleen volume reduction.

Question 382: Was a symptom response achieved?

The Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) is used to evaluate the recipient's symptom response. The MPN-SAF TSS is used to provide an accurate assessment of MPN symptom burden. The evaluation tool allows recipients with MPN to report their symptom severity at the worst level. They rate their symptom severity on a scale from zero to ten, zero being absent to ten being the worst imaginable. Adding the scores for all symptoms together will result in the recipient's MPN-SAF TSS. See Table 1 below for an example of this assessment:

Table 1. Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

Symptom	**1 to 10 (0 if absent) ranking – 1 is most favorable and 10 least favorable**
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours	(No fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms.	**—**

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Problems with concentration – Compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Numbness / tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst imaginable)

A symptom response is achieved when there is a ≥ 50% reduction in the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS).

Specify if a symptom response has been achieved at the last evaluation prior to preparative regimen / infusion.

Question 383: Date assessed

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen / infusion. 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.

Question 384: Specify the cytogenetic response

Specify the recipient's cytogenetic response at the last evaluation prior to the start of the preparative regimen / infusion.

If there is eradication of the previous reported abnormality select **Complete response (CR)**.

If there is a ≥ 50% reduction in abnormal metaphases, select **Partial Remission (PR)**.

Select **Re-emergence** of pre-existing cytogenetic abnormality if the cytogenetic abnormality was eradicated and reemerged at the last evaluation.

If cytogenetic response was not tested at the last evaluation, select **Not assessed** and continue with *Specify the molecular response*.

Select **Not applicable** if cytogenetic abnormalities were never identified and continue with *Specify the molecular response*.

If the recipient does not meet the criteria for **CR** or **PR**, select **None of the above** and continue with *Date assessed* (e.g., if a new cytogenetic abnormality is identified but there is also eradication of a previous abnormality).

Example: A recipient had 10 abnormal metaphases (out of 20) at diagnosis. At the last evaluation prior to the start of the preparative regimen, they had 2 abnormal metaphases (out of 20). As this is a ≥ 50% reduction in abnormal metaphases, Partial Remission (PR) should be reported.

Question 385: Date assessed

Report the date the cytogenetic response was established. Enter the date the sample was collected for pathologic evaluation (e.g., bone marrow biopsy) or blood/serum assessment (e.g., CBC, peripheral blood smear).

Question 386: Specify the molecular response

Specify the recipient's molecular response at the last evaluation prior to the start of the preparative regimen / infusion, based on the four drive mutations (JAK2, CALR, MPL, and CSF3R).

If there is eradication of the previously reported driver mutation (JAK2, CALR, MPL, and/or CSF3R), select **Complete response (CR)**.

If there is a 50% decrease in allele burden of the driver mutation (JAK2, CALR, MPL, and/or CSF3R), select **Partial Remission (PR)**.

Example: A recipient was found to have a molecular mutation identified (JAK2, CALR, MPL, and/or CSF3R) in 80% of cells examined at diagnosis. At their last evaluation prior to transplant, the molecular mutation was only identified in 40% of cells examined. The number of cells with the molecular mutation identified

decreased from 80% to 40%, which is a 50% reduction. In this case, “Partial Remission” should be reported as their molecular response.

Select **Re-emergence of pre-existing molecular abnormality** if the molecular abnormality (JAK2, CALR, MPL, and/or CSF3R) was eradicated and reemerged at the last evaluation.

Select **Not applicable** if JAK2, CALR, MPL, and CSF3R were never identified and go to first name.

If molecular response was not tested at the last evaluation select **Not assessed** and go to first name. If the recipient does not meet the criteria for **CR** or **PR**, select **None of the above** and go to first name.

Question 387: Date assessed

Report the date the molecular response was established. Enter the date the sample was collected for pathologic evaluation (e.g., bone marrow biopsy) or blood/serum assessment (e.g., CBC, peripheral blood smear).

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

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
279	2/12/ 2024	Add	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis in the Laboratory Studies at Diagnosis of MPN blue box: *Report laboratory results closest to the diagnosis date and prior to the start of first treatment of the primary disease for which the HCT is being performed. If the recipient’s MPN transformed, report the studies from the original diagnosis.*	Added for clarification
279	4/21/ 2023	Modify	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis.	To ensure more consistent reporting, all labs for the “at diagnosis” timepoint were clarified to reflect the values obtained closest to the date of diagnosis, prior to the start of any therapy.

317, 374	10/17/ 2023	Modify	~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality*.	Updated due to the enabling of the ISCN string data field with the Summer 2023 quarterly release:

Last modified: Feb 12, 2024

Q388 – 394: Other Leukemia

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

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 other leukemia is CLL and CLL transformed to DLBCL (Richter syndrome), report the diagnosis date of DLBCL and the primary disease for infusion as **Non-Hodgkin lymphoma** above. Ensure the Hodgkin / Non-Hodgkin Lymphoma section is completed. The CLL diagnosis is captured in the Hodgkin / Non-Hodgkin Lymphoma section.

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

Questions 388 – 389: Specify the other leukemia classification

Indicate the other leukemia disease classification at diagnosis. See below for general information about the other leukemia classifications listed on the form:

- **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.

If the subtype is not listed, report as **Other leukemia** and specify the disease.

Question 390: 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 C.

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 *Did a histologic transformation to diffuse large B-cell lymphoma (Richter syndrome) occur at any time after CLL diagnosis*. If **Yes**, and the disease classification is PLL, continue with to specify the disease status.

If cytogenetic studies did not detect any 17p abnormality at any time prior to the start of the preparative regimen, select **No**.

> **CLL with Richter's Transformation**
> If the recipient is receiving an infusion for CLL and there was a Richter's transformation to lymphoma, the primary disease for infusion should be reported as **Hodgkin lymphoma (150)** or **Non-Hodgkin's lymphoma (100)** and not **Other Leukemia (30)**.

Question 391: Did a histologic transformation to diffuse large B-cell lymphoma (Richter syndrome) occur at any time after CLL diagnosis?

Always report this question as **No.** This question will be updated in future releases. If CLL transformed, the primary disease should be reported as **Hodgkin lymphoma** or **Non-Hodgkin's lymphoma** – do not report the primary disease as **Other leukemia.**

Question 392: What was the disease status? (Atypical CML)

Indicate the disease status for atypical CML at the last evaluation prior the start of the preparative regimen (or infusion of no preparative regimen was given). If no treatment was given prior to HCT, select **No treatment** and submit the form.

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 393: What was the disease status? (CLL, PLL, Hairy cell leukemia, Other leukemia)

Indicate the disease status for CLL / SLL, PLL, hairy cell leukemia, or other leukemia at the last evaluation prior the start of the preparative regimen (or infusion if no preparative regimen was given). If no treatment was given prior to HCT, select Untreated and submit the form.

If reporting **CLL / SLL** or **PLL**, refer to the CLL Response Criteria section of the Forms Instructions Manual for definitions of each response.

Disease Status of Hairy Cell Leukemia[1]

Untreated
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 ≥ 11.0 g/dL (without transfusion)
- Platelets ≥ 100×10^9/L
- Absence of hairy cells on peripheral blood smear and on bone marrow examination

- No palpable lymphadenopathy or hepatosplenomegaly

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

Stable Disease (SD)
Not meeting the criteria for any of the other disease response criteria.

Progressive Disease
Requires one or more of the following:

- ≥ 25% increase in the absolute hairy cell count in the peripheral blood and/or bone marrow
- ≥ 25% decrease in any of the hematologic parameters (i.e., neutrophils, hemoglobin or platelets)
- ≥ 25% increase in abnormal lymphadenopathy or hepatosplenomegaly

Not assessed
No assessment of organomegaly, peripheral blood counts, absolute hairy cell count in the bone marrow or the peripheral blood smear was done at any time after treatment.

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

[1] 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 the CIBMTR Customer Service Center.

Question 394: 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.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
Q1	8/3/ 2023	Remove	Removed the word date: *Ensure the Hodgkin / Non-Hodgkin Lymphoma section is completed. The CLL diagnosis ~~date~~ is captured in the Hodgkin / Non-Hodgkin Lymphoma section.*	CLL diagnosis date is not captured in the Hodgkin / Non-Hodgkin Lymphoma section
Q391	10/17/ 2022	Add	Red instruction box added above Q391: ***CLL with Richter's Transformation*** *If the recipient is receiving an infusion for CLL and there was a Richter's transformation to lymphoma, the primary disease for infusion should be reported as* ***Hodgkin lymphoma (150)*** *or* ***Non-Hodgkin's lymphoma (100)*** *and not* ***Other Leukemia (30)****.*	Updated for clarification
Q391	10/17/ 2022	Modify	Instructions updated for clarification: ~~*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 the Hodgkin / Non-Hodgkin Lymphoma section. If*~~	Updated for clarification

			~~*CLL did not transform, select* **No** *and report the disease status.*~~ *Always report this question as* ***No.*** *This question will be updated in future releases. If CLL transformed, the primary disease should be reported as* ***Hodgkin lymphoma*** *or* ***Non-Hodgkin's lymphoma*** *– do not report the primary disease as* ***Other leukemia.***	

Last modified: Aug 03, 2023

Q395 – 412: Hodgkin and Non-Hodgkin Lymphoma

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.

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.

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)**.

> **Acute Lymphoblastic Leukemia / Lymphoma**
> Due to the aggressive nature of precursor B- and precursor T-cell lymphoblastic lymphoma (or lymphoma / leukemia), the primary disease to report for recipients with these malignancies should be acute lymphoblastic leukemia (B-cell lymphoblastic leukemia / lymphoma or early T-cell precursor lymphoblastic leukemia.

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 and most likely classified as “B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma”.

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 on the Pre-TED Form (Form 2400) or Pre-CTED (Form 4000).

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 269. Complete the Disease Classification questions for NHL. This only applies when the NHL and HL have been diagnosed at different times (i.e., two primaries).

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

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 lymphoma transformed from CLL, report the diagnosis date of the lymphoma. The CLL diagnosis will be captured below.

If the lymphoma transformed from a less severe lymphoma to a more severe lymphoma, report the diagnosis date of the more severe lymphoma. The initial lymphoma (i.e., less severe type) will be captured below.

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

DLBCL and Relapse with Follicular Lymphoma
In some scenarios, a recipient may be diagnosed with DLBCL and then later, relapses with Follicular lymphoma prior to infusion. In these cases, it is important to determine the primary disease for infusion with the physician. If the primary disease for infusion is **Follicular lymphoma**, report the diagnosis date as the date when the recipient was diagnosed with Follicular lymphoma (i.e., the relapse date) and report the lymphoma histology for infusion as 'Follicular lymphoma.' If the primary disease for infusion is **DLBCL**, report the diagnosis date as the date the recipient was diagnosed with DLBCL and report the lymphoma histology for infusion as 'DLBCL.'

Follicular Lymphoma Grade Progression
Follicular lymphoma may progress to a more severe grade prior to infusion (i.e., follicular lymphoma grade I to follicular lymphoma grade II); however, progression of the grade of follicular lymphoma should not be reported as a transformation. In cases where the follicular grade progresses, report the *most severe* follicular lymphoma grade (i.e., the follicular grade after progression) as the histology for infusion and report **No**, there was not a transformation – the initial follicular grade at diagnosis will not be captured on the Disease Classification (2402) Form.

Questions 395 – 396: Specify the lymphoma histology (at infusion)

Double-hit or triple-hit lymphomas – Rearrangements of MYC and BCL2 and/or BCL6 constitute a single category in the updated WHO classification and should be reported as **High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements** on CIBMTR forms.

Indicate the histology for which the recipient is receiving a transplant or cellular therapy. If the histology is **Other B-cell lymphoma** or **Other T-cell / NK-cell lymphoma**, specify the histology.

Continue with Assignment of DLBCL (germinal center B-cell type vs activated B-cell type) subtype was based on if either of the following histologies were reported as:

- **Diffuse, large B-cell lymphoma – Activated B-cell type (non-GCB)**
- **Diffuse, large B-cell lymphoma – Germinal center B-cell type**

Otherwise, continue with *Is the lymphoma histology reported at transplant a transformation from CLL*.

Question 397: Assignment of DLBCL subtype

DLBCL subtypes may be identified using different techniques including immunohistochemistry (IHC) and gene expression profiling. IHC involves staining a tissue sample and determining the presence of cell surface markers via microscopy. Gene expression profiling utilized molecular techniques.

Report the method used to determine the DLBCL subtype. Indicate **Unknown method** if the method cannot be determined from the available source documentation.

Question 398: Is the lymphoma histology reported at transplant 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. In a sub-set of CLL cases, the transformation may be to Hodgkin lymphoma (HL).

If the histology reported at infusion is a transformation from CLL, indicate **Yes**.

If the histology reported at infusion is not a transformation from CLL, indicate **No**.

Question 399: Was any 17p abnormality detected?

Report **Yes** if an abnormality was ever detected (by any method) on the short arm of chromosome 17 since the date of diagnosis of CLL. This includes any 17p abnormality detected after transformation to lymphoma. Report **No** if a 17p abnormality was not detected.

DLBCL and Relapse with Follicular Lymphoma

In some scenarios, a recipient may be diagnosed with DLBCL and then later, relapses with Follicular lymphoma prior to infusion. In these cases, it is important to determine the primary disease for infusion with the physician. If primary disease for infusion is **Follicular lymphoma**, report 'no' there was not a transformation. However, on the Pre-TED (2400) form, report there was a previous malignancy of lymphoma. If the primary disease for infusion is **DLBCL**, report 'yes' there was a transformation and the date of the original lymphoma diagnosis as the date when the recipient was diagnosed with DLBCL (i.e., question 1 and question 403 will be the same) as it is presumed Follicular lymphoma was present all along.

Follicular Lymphoma Grade Progression
Follicular lymphoma may progress to a more severe grade prior to infusion (i.e., follicular lymphoma grade I to follicular lymphoma grade II); however, progression of the grade of follicular lymphoma should not be reported as a transformation. In cases where the follicular grade progresses, report the *most severe* follicular lymphoma grade (i.e., the follicular grade after progression) as the histology for infusion and report **No**, there was not a transformation – the initial follicular grade at diagnosis will not be captured on the Disease Classification (2402) Form.

Question 400: Is the lymphoma histology reported at transplant a transformation from a different lymphoma histology (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**.

Questions 401 – 402: Specify the original lymphoma histology (prior to transformation)

Report the histology of the recipient's primary disease at diagnosis. If the histology is **Other B-cell lymphoma** or **Other T-cell / NK-cell lymphoma**, specify the histology.

Question 403: Date of original lymphoma diagnosis

Report the date of diagnosis for the histology specified in *Specify the original lymphoma histology (prior to transformation)*. If the exact pathological diagnosis date is not known, use the process described in General Instructions, General Guidelines for Completing Forms.

Cellular Therapy and PET (or PET / CT) at Last Evaluation
For cellular therapy infusions, a PET (or PET / CT) may be reported if the last scan was performed before leukapheresis, within three months of starting lymphodepleting therapy, even if additional therapy was given after the last scan.

Question 404: Was a PET (or combination PET / CT) scan performed? (at last evaluation prior to the start of the preparative regimen / infusion)

Report **Yes** if a PET scan was performed within three months prior to the start of the preparative regimen / infusion and meets the following criteria:

- Was performed within three months prior to the start of the preparative regimen / infusion and
- Was performed after the last pre-infusion line of therapy started

Combination PET / CT may also be reported, but a CT scan alone should not be captured here. Centers may report a PET scan performed during the most recent line of therapy so long as it is the most recent scan and was done within noted period. Report **No** if a PET scan was not performed within this period.

Question 405: Was the PET (or PET / CT) scan positive for lymphoma involvement at any disease site?

Report **Yes** if the most recent PET scan prior to the start of the preparative regimen / infusion detected the recipient's primary disease. Otherwise, report **No**.

Questions 406 – 407: Date of PET scan

If the date of this PET scan is known, report **Known** and specify the date. If the date is only partially known (e.g., the month and year are known, but not the day) report **Known**, and use the process described in General Instructions, General Guidelines for Completing Forms to complete question 391. If the date cannot be determined / estimated, report **Unknown**.

Questions 408 – 409: Deauville (five-point) score of the PET (or PET/CT) scan

Report whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If **Known**, report the score. Otherwise, report **Unknown**. If the PET scan result is only documented as an 'X', report this as **Unknown**.

If multiple scores are documented, report the highest. If a score is not documented within the PET (or PET/CT) scan report **Unknown** or work with the physician / radiologist to determine if a score can be reported. Do not determine Deauville scores without seeking physician / radiologist clarification.

> **DLBCL and Relapse with Follicular Lymphoma**
> In some scenarios, a recipient may be diagnosed with DLBCL and then later, relapses with Follicular lymphoma prior to infusion. In these cases, it is important to determine the primary disease for infusion with the physician. If primary disease for infusion is **Follicular lymphoma**, report the pre-infusion disease status since the diagnosis of the Follicular lymphoma (not since the diagnosis of DLBCL). If the primary disease for infusion is **DLBCL**, report the pre-infusion disease status since the original diagnosis of DLBCL.

Question 410: What was the disease status?

The recipient's pre-HCT disease status may be evaluated by a PET scan, CT scan, or both. If possible,

report the disease status using the metabolic (PET) criteria provided in the Lymphoma Response Criteria section of the manual. If it is not possible to use metabolic criteria to report the recipient's disease (e.g., insufficient PET scan(s), non-PET-avid disease), use the radiographic criteria instead.

If metabolic criteria are used to determine the pre-HCT disease status, per the IWG criteria, normal morphology of the bone marrow is not required for reporting complete remission.

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. When a transformation has occurred (e.g., follicular lymphoma (FL) transformed to DLBCL), count the response number (CR1, REL2, etc.) beginning with the transformed lymphoma (in this case the DLBCL). Do not include the responses to the lymphoma sub-type prior to the transformation.

Question 411: Total number of lines of therapy received (between diagnosis and HCT / infusion)

A single line of therapy refers to any agents administered during the same time period with the same intent (induction, consolidation, etc.). If a recipient's disease status changes resulting in a change to treatment, this should be considered a new line of therapy. Additionally, if therapy is changed because a favorable disease response was not achieved, this should be considered a new line of therapy. Do not include surgery when determining the number of lines of therapy.

Report the total number of lines of therapy received since the original lymphoma diagnosis up until the start of the preparative regimen / infusion, regardless of if the recipient has received a prior infusion. If there was a transformation (lymphoma transformation or Richter's transformation), include lines of therapy given to treat the original lymphoma histology or CLL prior to transformation.

Example 1: A recipient received a line of induction and achieved CR. However, following induction, the recipient relapsed and received a line of re-induction with no response. After re-induction, the recipient transformed, received a different line of re-induction followed by consolidation and achieved CR2 prior to HCT. This would be considered as four separate lines of therapy and the total number of lines of therapy reported in this example would be "3+ lines."

Example 2: A recipient received a line of induction, achieved CR, and then went to HCT. Post-transplant, the recipient transformed, received a line of re-induction followed by a line of consolidation and achieved CR2 prior to the second HCT. In this scenario, the recipient received three lines of therapy and "3+ lines" would be reported.

Question 412: 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, General Guidelines for Completing Forms.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
Q1	8/3/ 2023	Remove	Removed the word date: *If the lymphoma transformed from CLL, report the diagnosis date of the lymphoma. The CLL diagnosis ~~date~~ will be captured below.*	CLL diagnosis date is not captured in the Hodgkin / Non-Hodgkin Lymphoma section
Q395	5/2/ 2023	Add	The Follicular Lymphoma Grade Progression blue box added above Q395: ***Follicular Lymphoma Grade Progression****: Follicular lymphoma may progress to a more severe grade prior to infusion (i.e., follicular lymphoma grade I to follicular lymphoma grade II); however, progression of the grade of follicular lymphoma should not be reported as a transformation. In cases where the follicular grade progresses, report the most severe follicular lymphoma grade (i.e., the follicular grade after progression) as the histology for infusion and report* ***No****, there was not a transformation – the initial follicular grade at diagnosis will not be captured on the Disease Classification (2402) Form.*	Added for clarification
Q400	5/2/ 2023	Add	The Follicular Lymphoma Grade Progression blue box added above Q400:***Follicular Lymphoma Grade Progression****: Follicular lymphoma may progress to a more severe grade prior to infusion (i.e., follicular lymphoma grade I to follicular lymphoma grade II); however, progression of the grade of follicular lymphoma should not be reported as a transformation. In cases where the follicular grade progresses, report the most severe follicular lymphoma grade (i.e., the follicular grade after progression) as the histology for infusion and report* ***No****, there was not a transformation – the initial follicular grade at diagnosis will not be captured on the Disease Classification (2402) Form.*	Added for clarification
Q408	2/13/ 2024	Add	Instructions updated to clarify Deauville scores should not be determined without physician / radiologist clarification: *Report*	Added for clarification

			*whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If **Known**, report the score. Otherwise, report **Unknown**. If the PET scan result is only documented as an 'X', report this as **Unknown**. If multiple scores are documented, report the highest. If a score is not documented within the PET (or PET/CT) scan, work with the physician / radiologist to determine if a score can be reported. Do not determine Deauville scores without seeking physician / radiologist clarification.*	
Q408	2/13/ 2024	Add	Instructions updated to clarify Deauville scores should not be determined without physician / radiologist clarification: *Report whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If **Known**, report the score. Otherwise, report **Unknown**. If the PET scan result is only documented as an 'X', report this as **Unknown**. If multiple scores are documented, report the highest. If a score is not documented within the PET (or PET/CT) scan, work with the physician / radiologist to determine if a score can be reported. Do not determine Deauville scores without seeking physician / radiologist clarification.*	Added for clarification
Q408	2/13/ 2024	Add	Instructions updated to clarify Deauville scores should not be determined without physician / radiologist clarification: *Report whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If **Known**, report the score. Otherwise, report **Unknown**. If the PET scan result is only documented as an 'X', report this as **Unknown**. If multiple scores are documented, report the highest. If a score is not documented within the PET (or PET/CT) scan, work with the physician / radiologist to determine if a score can be reported. Do not determine Deauville scores without seeking physician / radiologist clarification.*	Added for clarification
Q408	2/23/ 2024	Add	Instructions updated to clarify Deauville scores should not be determined without physician / radiologist clarification: *Report whether the five-point PET score is known. This information is typically documented in the PET report. Consult the appropriate transplant physician if the results are unclear. If **Known**, report the score. Otherwise, report **Unknown**. If the PET scan result is only documented as an 'X', report this as **Unknown**. If multiple scores are documented, report the highest. If a score is not*	Added for clarification

			documented within the PET (or PET/CT) scan, report ***Unknown*** *or work with the physician / radiologist to determine if a score can be reported. Do not determine Deauville scores without seeking physician / radiologist clarification.*	
Q411	5/1/ 2023	Add	Instructions added on how to report lines of therapy when there was a Richter's transformation: *A single line of therapy refers to any agents administered during the same time period with the same intent (induction, consolidation, etc.). If a recipient's disease status changes resulting in a change to treatment, this should be considered a new line of therapy. Additionally, if therapy is changed because a favorable disease response was not achieved, this should be considered a new line of therapy. Do not include surgery when determining the number of lines of therapy. Report the total number of lines of therapy received since the original lymphoma diagnosis up until the start of the preparative regimen / infusion, regardless of if the recipient has received a prior infusion. If there was a transformation (lymphoma transformation or Richter's transformation), include lines of therapy given to treat the original lymphoma histology or CLL prior to transformation.*	Added for clarification

Last modified: Feb 23, 2024

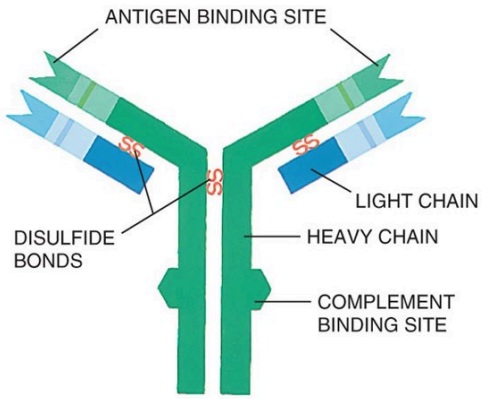
Q413 – 459: Multiple Myeloma / Plasma Cell Disorder

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 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.

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the diagnosis date as the first date when all diagnostic criteria for the multiple myeloma / PCD subtype is met. Refer to the criteria listed below for symptomatic multiple myeloma. For other multiple myeloma / PCD subtypes, refer to the guidelines listed in the Disease Assessments at Diagnosis section of the PCD Pre-Infusion manual.

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

*Multiple Myeloma (symptomatic)[4]
Diagnostic criteria for symptomatic multiple myeloma require clonal bone marrow plasma cells in ≥ 10% or biopsy proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:

1. Evidence of end organ damage (i.e., CRAB features) that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >1 mg/dL (> 0.25 mmol/L) higher than the ULN or > 11 mg/dL (> 2.75 mmol/L)
- Renal insufficiency: creatinine clearance < 40 ml/min or serum creatinine > 2 mg/dL (> 177 µmol/L)
- Anemia: hemoglobin > 2 g/dL (> 20 g/L) below the LLN or a hemoglobin < 10 g/dL (< 100 g/L)
- Bone lesions: one or more osteolytic lesions on skeletal x-ray, CT or PET-CT

2. Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage ≥ 60%
- Involved : uninvolved serum free light chain ratio ≥ 100
- > 1 focal lesions on MRI studies (each lesion must be ≥ 5 mm in size)

[4] (2015, October 29). International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma. Retrieved February 15, 2017, from http://imwg.myeloma.org/international-myeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiple-myeloma/

Questions 413 – 414: 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.

Plasma Cell Disorders and Characteristics

Multiple Myeloma (symptomatic)[4]

Diagnostic criteria for symptomatic multiple myeloma requires clonal bone marrow plasma cells in ≥ 10% or biopsy proven bony or extramedullary plasmacytoma and any one or more of the following myeloma-defining events:

1. Evidence of end organ damage (i.e., CRAB features) that can be attributed to the underlying plasma cell proliferative disorder, specifically:

- Hypercalcemia: serum calcium >1 mg/dL (> 0.25 mmol/L) higher than the ULN or > 11 mg/dL (> 2.75 mmol/L)
- Renal insufficiency: creatinine clearance < 40 ml/min or serum creat >2 mg/dL (> 177 µmol/L)
- Anemia: hemoglobin > 2 g/dL (> 20 g/L) below the LLN or a hemoglobin <10 g/dL (< 100 g/dL)
- Bone lesions: one or more osteolytic lesions on skeletal x-ray, CT or PET-CT

2. Any one or more of the following biomarkers of malignancy:

- Clonal bone marrow plasma percentage ≥ 60%
- Involved **:** uninvolved serum free light chain ratio ≥ 100
- > 1 focal lesion on MRI studies (each lesion must be ≥ 5 mm in size)

[4] (2015, October 29). International Myeloma Working Group (IMWG) Criteria for the Diagnosis of Multiple Myeloma. Retrieved February 15, 2017, from http://imwg.myeloma.org/international-myeloma-working-group-imwg-criteria-for-the-diagnosis-of-multiple-myeloma/

Plasma Cell Leukemia

- Peripheral blood absolute plasma cell count of at least 2.0 × 10^9/L (2,000 cells/mm^3)
- ≥ 20% plasma cells in the peripheral differential white blood cell count.[5]

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)[5]

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[6]
- Castleman disease[6]
- Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)
- Edema (edema, pleural effusion, or ascites)
- Endocrinopathy (adrenal, thyroid[7], pituitary, gonadal, parathyroid, pancreatic[7])
- Skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, white nails)
- Papilledema

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.[8]

[5] 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.

[6] Osteosclerotic lesion or Castleman disease is usually present.

[7] Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion. Dispenzieri A, Kyle RA, Lacy MQ, et al. POEMS syndrome: definitions and long-term outcome. *Blood*. 2003;101(7):2496-506.

[8] UNC Kidney Center, University of North Carolina. Light Chain Deposition Disease. 5 Apr. 2013. Accessed at: http://unckidneycenter.org/kidneyhealthlibrary/glomerular-disease/light-chain-deposition-disease Accessibility verified on January 30, 2017

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 415.

- Multiple myeloma – IgG
- Multiple myeloma – IgA
- Multiple myeloma – IgD
- Multiple myeloma – IgE
- Multiple myeloma – IgM (not Waldenstrom macroglobulinemia)
- Multiple myeloma – light chain only

If the recipient's disease classification is the following, continue with question 416.

- Amyloidosis

If the recipient's disease classification is the following, continue with question 417.

- Monoclonal gammopathy of renal significance (MGRS)

If the recipient's disease classification is the following, continue with question 420.

- Solitary plasmacytoma (no evidence of myeloma)

If the recipient's disease classification is the following, neither kappa nor lambda light chains will be present; therefore, continue with question 421.

- Multiple myeloma – non-secretory

If the recipient's disease classification is one of the following, continue with question 423.

- Plasma cell leukemia
- Smoldering myeloma
- Osteosclerotic myeloma/POEMS syndrome

If the recipient's disease classification is the following, continue with question 414.

- Other Plasma Cell Disorder

Question 415: Specify heavy and / or light chain type (check all that apply)

Indicate the heavy and / or light chain type for the recipient's disease. Select all that apply.

More than one heavy and / or light chain should only be selected for recipients diagnosed with bi-clonal multiple myeloma.

Question 416: Specify Amyloidosis classification

Specify the amyloidosis classification as one of the following:

- **AL amyloidosis** (light-chain amyloidosis): This is the most common type of amyloidosis where the abnormally folded protein is the light chain component of an immunoglobulin. Misfolded proteins can deposit in the nervous system, heart, kidneys, or digestive tract; however they can often affect more than one organ.[9]
- **AH amyloidosis** (heavy-chain amyloidosis): This is a rare type of amyloidosis where the abnormally folded protein is the heavy chain component of an immunoglobulin.[10]
- **AHL amyloidosis** (heavy- and light-chain amyloidosis): This is a rare type of amyloidosis where the abnormally folded protein is composed of fragments of both the Ig heavy chain and light chain.[10]

fn9."AL Amyloidosis." Amyloidosis Foundation, http://amyloidosis.org/facts/al/.

[10] Nasr, S. H. (2013). The diagnosis and characteristics of renal heavy-chain and heavy/light-chain amyloidosis and their comparison with renal light-chain amyloidosis. Kidney International, 83(3), 463–470. https://doi.org/10.1038/ki.2012.414

Question 417: Select monoclonal gammopathy of renal significance (MGRS) classification

Specify the monoclonal gammopathy of renal significance (MGRS) classification. If the classification reported is* Monoclonal immunoglobulin deposition disease (MIDD)*, report the MIDD disease subtype.

Question 418: Select monoclonal immunoglobulin deposition disease (MIDD) subtype

Specify the Monoclonal immunoglobulin deposition disease (MIDD) subtype as one of the following:

- **Light chain deposition disease (LCDD)**
- **Light and heavy chain deposition disease (LHCDD)**
- **Heavy chain deposition disease (HCDD)**

Question 419: Was documentation submitted to the CIBMTR? (e.g. pathology report)

Indicate if a pathology report is attached to support the MGRS classification reported above. For further

instructions on how to attach documents in FormsNet3[SM], refer to the Training Guide.

Question 420: Solitary plasmacytoma was

Indicate if the solitary plasmacytoma was **Bone derived** or **Extramedullary**. Refer to the Plasma Cell Characteristics above for additional information regarding the characteristics of each type.

> **Durie-Salmon staging:** If this form is being completed for a subsequent infusion, report the Durie-Salmon staging at the time of the multiple myeloma diagnosis, and not at the time of relapse or progression.

Question 421: What was the Durie-Salmon staging (at diagnosis)?

Indicate Durie-Salmon staging at diagnosis. If the Durie-Salmon stage is not documented in the medical record, use the table below to determine the appropriate stage.

The Durie-Salmon stage is only required if the recipient's I.S.S. stage at diagnosis cannot be determined and is not reported below.

If the Durie-Salmon stage is unknown and cannot be determined using the table below, select **Unknown**.

Question 422: What was the Durie-Salmon sub classification (at diagnosis)?

Indicate the Durie-Salmon sub classification at diagnosis. If the Durie-Salmon sub classification is not documented in the medical record, use the criteria below to determine the appropriate sub classification.

A: Relatively normal renal function (serum creatinine < 2.0 mg/dL)
B: Abnormal renal function (serum creatinine ≥ 2.0 mg/dL)

Durie-Salmon Staging System for Multiple Myeloma[8]

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)

[8] 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.

Question 423: Did the recipient have a preceding or concurrent plasma cell disorder?

Indicate if the recipient had a concurrent or preceding plasma cell disorder. Many recipients progress to symptomatic myeloma from a preceding condition or have a concurrent plasma cell disorder, such as amyloidosis.

Example 1. If a recipient has smoldering myeloma (asymptomatic) and then develops symptomatic multiple myeloma, “multiple myeloma” should be reported as the primary diagnosis in question 397 and “smoldering myeloma” should be reported as the preceding / concurrent disorder.

Example 2. If a recipient has smoldering myeloma (asymptomatic) and amyloidosis, “amyloidosis” should be reported as the primary diagnosis in question 397 and “smoldering myeloma” should be reported as the preceding / concurrent disorder.

Example 3. If the recipient has symptomatic multiple myeloma and amyloidosis, “multiple myeloma” should be reported as the primary diagnosis in question 397 and “amyloidosis” should be reported as the preceding / concurrent disorder.

Reporting More Than One Concurrent or Preceding Disorder
Copy *Specify preceding / concurrent disorder* and *Date of diagnosis of preceding / concurrent disorder* questions to report more than one concurrent or preceding disorder.

Questions 424 – 425: Specify preceding / concurrent disorder

Indicate the preceding or concurrent disorder. See the Plasma Cell Characteristics information above for descriptions of disease and the previous question for examples of situations with preceding or concurrent disorders. If the recipient has a preceding or concurrent plasma cell disorder that is not listed, select **Other plasma cell disorder (PCD)** and specify the type.

Question 426: Date of diagnosis or preceding / concurrent disorder

Report the date the recipient was first diagnosed with the preceding or concurrent plasma cell disorder. Enter the date the blood/urine was collected for the laboratory evaluations (e.g., serum/urine protein

electrophoresis [SPEP/UPEP, respectively], or serum/urine immunofixation) or enter the date of the first pathological diagnosis (e.g., bone marrow biopsy, plasmacytoma, tissue). Enter the date the sample was collected for examination.

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

Copy questions 408-410 to report more than one concurrent or preceding disorder.

Assessments at diagnosis:
Questions 427 – 455 refer to the labs and assessments performed at diagnosis of the primary disease for transplant. All values reported must reflect testing performed prior to the start of first treatment of the primary disease for HCT.

Serum β2 microglobulin and albumin
If this form is being completed for a subsequent infusion, report the serum β2 microglobulin and albumin at the time of the multiple myeloma diagnosis, and not at the time of relapse or progression

Questions 427 – 428: Serum β2 microglobulin

At the time of plasma cell disorder diagnosis, an elevated β2 microglobulin protein may indicate a poorer prognosis. Indicate whether the β2 microglobulin protein was **Known** or **Unknown** at the time of plasma cell disorder diagnosis. If this value was **Known**, report the value and unit of measure documented on the laboratory report.

Questions 429 – 430: Serum albumin

Indicate whether the serum albumin was **Known** or **Unknown** at the time of plasma cell disorder diagnosis. If **Known**, report the value and unit of measure documented on the laboratory report.

I.S.S. and R-I.S.S. staging
If this form is being completed for a subsequent infusion, report the I.S.S. and R-I.S.S. staging at the time of the multiple myeloma diagnosis, and not at the time of relapse or progression.

Questions 431 – 432: Stage at Diagnosis: I.S.S.

Report the recipient's ISS stage of myeloma at diagnosis.

I.S.S. Staging System for Multiple Myeloma[11]

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

[11] 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.

Questions 433 – 434: Stage at Diagnosis: R – I.S.S.

The Revised International Staging System (R-ISS) includes variables included in the original ISS (serum beta-2 microglobulin and serum albumin), while also including the additional prognostic information obtained from serum LDH and high-risk chromosomal abnormalities detected by interphase fluorescent in situ hybridization (iFISH) after CD138 plasma cell purification.[12] High risk chromosomal abnormalities identified by iFISH include:

- Deletion 17p / 17p-
- t(4;14)
- t(14;16)

Report the recipient's R-ISS stage of myeloma at diagnosis

R-I.S.S. Staging System for Multiple Myeloma[12]

Stage	Description
Stage I	ISS stage I and standard-risk chromosomal abnormalities identified by iFISH and normal LDH
Stage II	Not R-ISS stage I or III
Stage III	ISS stage III and either high-risk chromosomal abnormalities identified by iFISH or high LDH

[12] Palumbo, A. et al (2015). Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol, 33(26), 2863-9. doi: 10.1200/JCO.2015.61.

Questions 435 – 436: Plasma cells in peripheral blood by flow cytometry

Indicate if plasma cells in the peripheral blood by flow cytometry was **Known** or **Unknown** at the time of diagnosis. If **Known**, report the percentage of plasma cells detected in the blood by flow cytometry documented on the flow cytometry report.

Questions 437 – 439: Plasma cells in peripheral blood by morphologic assessment

Indicate if plasma cells in the peripheral blood by morphologic assessment was **Known** or **Unknown** at the time of diagnosis. If **Known**, report the percentage of plasma cells detected in the blood by morphologic assessment and / or the absolute number as documented on the laboratory report.

If a differential was performed and the percentage of plasma cells are not listed, report **Known** and specify the plasma cell percentage as “0”.

If only the percentage of plasma cells is available, the absolute number of plasma cells can be determined by multiplying the percentage of plasma cells by the white blood count (WBC).

Questions 440 – 442: LDH

Indicate whether the LDH (lactate dehydrogenase) level was **Known** or **Unknown** at the time of plasma cell disorder diagnosis. If **Known**, report the value and unit of measure documented on the laboratory report, and specify the upper limit of normal for LDH value and the unit of measure used at your institution.

Question 443: Were cytogenetics tested (karyotyping or FISH)? (at diagnosis)

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing blood or bone marrow for the presence of a known chromosomal abnormality which 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 C.

Karyotyping is performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are then performed to visualize the chromosomes during cell division so that various bands and reconfigurations can be seen. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

FISH is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA. These probes are mixed with cells from the recipient’s blood or bone marrow. A fluorescent “tag” is then used to visualize the binding of the probe to the diseased cells.

Indicate whether cytogenetic studies were performed at diagnosis. If cytogenetic studies were performed at diagnosis, check **Yes**. If cytogenetic studies were not obtained at diagnosis, or it is not known whether chromosome studies were performed, indicate **No** or **Unknown**, respectively.

Questions 444 – 445: Were cytogenetics tested via FISH? (at diagnosis)

If FISH studies were performed at diagnosis, report **Yes** and indicate whether clonal abnormalities were detected. If multiple FISH assessments were performed, report Abnormalities Identified if any testing showed clonal abnormalities at diagnosis. If FISH studies were not performed at diagnosis, FISH samples were inadequate, or it is unknown if performed, report **No**.

Report chromosomal microarrays / chromosomal genomic arrays as FISH assessments.

> ! The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time.

Questions 446 – 448: Specify cytogenetic abnormalities (FISH) (at diagnosis)

Report the ISCN compatible string, if applicable.
Select all cytogenetic abnormalities identified by FISH assessments at diagnosis.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 449: Was documentation submitted to the CIBMTR? (e.g. FISH report)

Indicate if a FISH report is attached to support the cytogenetic findings reported. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Questions 450 – 451: Were cytogenetics tested via karyotyping? (at diagnosis)

Indicate if karyotyping studies were performed at diagnosis. If Yes, indicate specify the results. If multiple karyotype assessments were performed at diagnosis, select Abnormalities identified if any testing showed clonal abnormalities. If the karyotype yielded no evaluable metaphase cells, select No evaluable metaphases.

If karyotyping studies were not performed at diagnosis or is unknown if performed, report No.

Questions 452 – 454: Specify cytogenetic abnormalities (karyotyping) (at diagnosis)

Report the ISCN compatible string, if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.

Select all cytogenetic abnormalities identified by karyotyping assessments at diagnosis by checking all abnormalities that apply.

If a clonal abnormality is detected, but not listed as an option, select **Other abnormality** and specify the abnormality. If multiple other abnormalities were detected, report “see attachment” and attach the final report(s) for any other abnormalities detected. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 455: Was documentation submitted to the CIBMTR? (e.g. karyotyping report)

Indicate if a karyotyping report is attached to support the cytogenetic findings reported. For further instructions on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 456: 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 the Multiple Myeloma Response Criteria section for multiple myeloma and solitary plasmacytoma disease status definitions. See Plasma Cell Leukemia Response Criteria for plasma cell leukemia disease status definitions.

This question will not be enabled if the primary disease for transplant is monoclonal gammopathy of renal significance (MGRS).

Question 457: 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. Date of radiographic study (PET, MRI, CT) may be used ***if*** the same radiographic study had previously 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, General Guidelines for Completing Forms.

Question 458: Specify amyloidosis hematologic response (for Amyloid patients only)

Indicate the disease status of amyloidosis at the last evaluation prior to the start of the preparative regimen. See the Amyloidosis Response Criteria section for disease status definitions.

If therapy was not given to treat amyloidosis, report **Unknown**.

Question 459: 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., free light chain ratio, serum / urine immunofixation) or report the date the bone marrow was collected for pathological evaluation.

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

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
415	2/12/ 2024	Add	Instructions clarified when to report more than one heavy / light chain: *Indicate the heavy and / or light chain type for the recipient's disease.*	Added for clarification.

			Select all that apply. More than one heavy and / or light chain type should only be selected for recipients diagnosed with biclonal multiple myeloma.	
452	10/17/ 2023	Modify	~~*The International System for Human Cytogenetic Nomenclature (ISCN) compatible string is disabled and cannot be answered at this time*~~ *Report the International System for Human Cytogenetic Nomenclature (ISCN) compatible string if applicable. Refer to Appendix C for more information on how to report using the ISCN functionality.*	Updated due to the enabling of the ISCN string data field with the Summer 2023 quarterly release.
427	4/21/ 2023	Modify	Clarified the instructions for the labs at diagnosis should reflect the labs closest to the date of diagnosis.	To ensure more consistent reporting, all labs for the “at diagnosis” timepoint were clarified to reflect the values obtained closest to the date of diagnosis, prior to the start of any therapy.

Last modified: Feb 12, 2024

Q460 – 461: Solid Tumors

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

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

Questions 460 – 461: 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. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Section Updates:

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

Last modified: Sep 23, 2022

Q462 – 464: Severe Aplastic Anemia

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

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

Questions 462 – 464: Specify the aplastic anemia classification

Indicate the aplastic anemia classification of the primary disease for infusion.

If any of the following classifications are selected:

- **Acquired AA, not otherwise specified (301)**
- **Acquired AA secondary to chemotherapy (313)**
- **Acquired AA secondary to hepatitis (302) (any form of hepatitis)**
- **Acquired AA secondary to immunotherapy or immune effector cell therapy (314)**
- **Acquired AA secondary to toxin / other drug (303)**

then, specify the severity below as either **Severe / Very Severe** or **Not Severe** at the time of diagnosis using the following criteria:

- **Severe / Very Severe** Requires both of the following[1]:
  - Bone marrow cellularity < 25% (or 25% to 50% if < 30% of residual cells are hematopoietic) *and*
  - At least two of the following:
    - Peripheral blood absolute neutrophil count (ANC) < 500 / µL (<0.5 x 10^9/L)
    - Peripheral blood platelet count < 20,000 / µL
    - Peripheral blood reticulocyte count < 20,000 / µL

- **Not severe**: Does not meet the criteria for **Severe / Very Severe**

[1] Olson, T. S. (2019, July 18). Aplastic anemia: pathogenesis, clinical manifestations, and diagnosis. UpToDate. https://www-uptodate-com/contents/aplastic-anemia-pathogenesis-clinical-manifestations-and-diagnosis?search=aplastic+anemia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=

Select **Acquired AA secondary to chemotherapy** only when a recipient develops acquired AA after receiving chemotherapy. See example below:

Example: A female recipient in her 50's was diagnosed with Stage IV breast cancer and received dose-dense chemotherapy with doxorubicin and cyclophosphamide every other week, followed by weekly Taxol. After receiving four cycles, the recipient became neutropenic requiring red blood cell and platelet transfusions. The chemotherapy was discontinued but the blood counts remained low. After three months of persistent neutropenia, the decision was made to proceed with transplant and the recipient was diagnosed with acquired AA secondary to chemotherapy.

If the classification is not listed, select **Other acquired cytopenic syndrome** and specify the other acquired cytopenic syndrome.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
462-464	9/28/ 2023	Modify	• ***Severe / Very Severe*** *Requires ~~two of more~~ both of the following*[1]: ◦ *Bone marrow cellularity < 25% (or 25% to 50% if < 30% of residual cells are hematopoietic)* *and* ◦ *At least two of the following:* ▪ *Peripheral blood absolute neutrophil count (ANC) < 500 / µL (<0.5 x 10^9/L)* ▪ *Peripheral blood platelet count < 20,000 / µL* ▪ *Peripheral blood reticulocyte count < 20,000 / µL*	Updated manual language for better clarification of severe / very severe Aplastic Anemia criteria

Last modified: Sep 28, 2023

Q465: Inherited Bone Marrow Failure Syndromes

Note: Primary Disease for Infusion: If the recipient was diagnosed with an inherited bone marrow failure syndrome and developed MDS or AML, report the primary disease for infusion as MDS or AML, respectively.

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of genetic / molecular testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Questions 465: Specify the inherited bone marrow failure syndrome classification

Indicate the inherited bone marrow failure syndrome classification of the primary disease for infusion.

- **Diamond-Blackfan anemia**: A rare genetic disorder that affects the ability of the marrow from producing red blood cells. These recipients may present with anemia but may also exhibit physical abnormalities such as: small head size, cleft lip, webbed neck, defects of the hands and a short stature.

  If **Diamond-Blackfan anemia** is selected and the recipient is randomized to the Comprehensive Report Form (CRF) track, the Aplastic Anemia Pre- and Post-Infusion (2028 / 2128) forms will come due.

- **Dyskeratosis congenita**: A genetic form of a bone marrow failure where the recipient is unable to produce sufficient blood cells. Subdivisions of dyskeratosis congenita includes dyskeratosis congenita (autosomal dominant), Scoggins type, dyskeratosis congenita (autosomal recessive), dyskeratosis congenita (X-linked), Zinsser-Cole-Engleman syndrome, Hoyeraal-Hreidarsson syndrome, and Revesz syndrome.

  If **Dyskeratosis congenita** is selected and the recipient is randomized to the Comprehensive Report Form (CRF) track, the Aplastic Anemia Pre- and Post-Infusion (2028 / 2128) forms will come due.

- **Fanconi anemia**: 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 recipients are short in stature, exhibit skeletal abnormalities, and have an increased risk of developing solid tumors, MDS, and leukemias.

  If **Fanconi anemia** is selected and the recipient is randomized to the Comprehensive Report Form (CRF) track, the Fanconi Pre- and Post-Infusion (2029 / 2129) forms will come due.

- **Severe congenital neutropenia**: A rare group of disorders that are characterized by neutropenia. These disorders are present at birth. Kostmann syndrome is included in this disease classification.

  If **Severe congenital neutropenia** is selected and the recipient is randomized to the Comprehensive Report Form (CRF) track, no disease specific forms will come due.

- **Shwachman-Diamond syndrome**: A rare autosomal recessive disorder which is characterized by exocrine pancreatic insufficiency, bone marrow dysfunction, and skeletal abnormalities.

  If **Shwachman – Diamond** is selected and the recipient is randomized to the Comprehensive Report Form (CRF) track, the Aplastic Anemia Pre- and Post-Infusion (2028 / 2128) forms will come due.

If the primary disease for infusion is not listed, select **Other inherited bone marrow failure syndrome.**

Section Updates:

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

Last modified: Sep 23, 2022

Q466 – 501: Hemoglobinopathies

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of genetic / molecular testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Questions 466 – 468: Specify the hemoglobinopathy classification

Indicate the hemoglobinopathy classification of the primary disease for infusion.

> **Sickle cell disease:** A group of disorders that adversely affect the body's production of hemoglobin, the component in red blood cells that delivers oxygen throughout the body. Individuals with these disorders possess atypical hemoglobin molecules, called hemoglobin "S," which can distort the red blood cell morphology into a sickle, or crescent, shape.
>
> **Transfusion dependent thalassemia:** Previously described as "beta thalassemia major" on CIBMTR forms. Transfusion-dependent thalassemia is a blood disorder that reduces the production of hemoglobin in the body and is defined as requiring eight or more transfusion events per year for two years or more for treatment of symptomatic anemia.
>
> If **Transfusion dependent thalassemia** is selected, specify the transfusion dependent thalassemia as either **Transfusion dependent beta thalassemia** (known as "beta thalassemia major" on prior CIBMTR forms) or **Other transfusion dependent thalassemia**.
>
> **Other hemoglobinopathy:** If the recipient is diagnosed with a hemoglobinopathy other than sickle cell disease or transfusion dependent thalassemia, select **Other hemoglobinopathy** and specify the type.

Questions 469 – 471: Was tricuspid regurgitant jet velocity (TRJV) measured by echocardiography?

Tricuspid regurgitant jet velocity (TRJV) measurements are used in determining the pulmonary artery pressure for patients with hemolytic disorders. An elevated TRJV is an indication of pulmonary hypertension, a condition common in adults with hemolytic diseases. TRJV can be determined by echocardiography (ECHO); this information is typically documented in the echocardiogram report.

Report whether the TRJV was measured by echocardiography prior to the start of the preparative regimen / infusion. Seek physician clarification, as needed, if the results are unclear.

If the TRJV was measured by echocardiography, select **Yes** and indicate if the TRJV value is **Known** or **Unknown**. If **Known**, specify the TRJV value documented in the laboratory report. If the TRJV was measure multiple times prior to the start of the preparative regimen / infusion by an echocardiography, report the most recent value.

If the TRJV was not measured or it is not known if measured by echocardiography at the diagnosis of transfusion dependent thalassemia, report **No** or **Unknown**, respectively.

Questions 472 – 474: Was liver iron content (LIC) tested within 6 months prior to infusion?

Transfusion support for hemolytic diseases can often lead to iron build up or accumulation in the liver and other target organs. Liver iron content (LIC) is commonly used to measure total iron storage for recipients at risk of hemosiderosis. LIC is a more sensitive method of testing for measuring the level of iron in the liver. Common methods include, but are not limited to, liver biopsy, T2*MRI, and FerriScan.

Report **Yes** if the liver iron content was assessed within six months prior to the start of the preparative regimen / infusion. Report the value and unit of measure documented in the laboratory report. Also report the method used to estimate the LIC. If the method of assessment is not listed, select **Other**.

Report **No** if liver iron content was not assessed or it is not known if assessed within six months prior to the start of the preparative regimen / infusion.

Questions 475 – 476: Is the recipient red blood cell transfusion dependent?

Indicate if the recipient is red blood cell transfusion dependent at any time prior to the start of the preparative regimen / infusion. In this context, “red blood cell transfusion dependent” is defined as requiring transfusions to maintain hemoglobin 9 – 10 d / dL.

If the recipient the recipient was red blood cell transfusion dependent at any time prior to the start of the preparative regimen / infusion, report **Yes** and specify the year of the first transfusion (since diagnosis).

If the recipient was never red blood cell transfusion dependent at any time prior to the start of the preparative regimen / infusion, report **No**.

Question 477: Was iron chelation therapy given at any time since diagnosis?

Iron chelation therapy is commonly used for recipients to prevent or reduce iron overload. Iron chelation therapy is the removal of excess iron from the body using drugs such as Deferrioxamine (Desferal) or Deferasirox (Jadenu, Exjade).

Select **Yes** if iron chelation therapy was given at any time since diagnosis. If iron chelation was not given or it is unknown whether iron chelation therapy was given, select **No** or **Unknown**, respectively.

Question 478: Did iron chelation therapy meet the following criteria: initiated within 18 months of the first transfusion and administered for at least 5 days / week (either oral or parenteral iron chelation medication)

Indicate if the iron chelation therapy was initiated within 18 months of the first transfusion and administered for at least five days a week (either oral or parenteral iron chelation medication).

If iron chelation therapy met the criteria listed above, report **Yes, iron chelation therapy given as specified**.

If iron chelation therapy was given but does not meet the specified criteria, report **No, iron chelation therapy given, but does not meet criteria**.

If iron chelation therapy was given but administration details are unavailable, report **Iron chelation therapy given, but details of administration unknown**.

Questions 479 – 480: Specify reason criteria not met

If iron chelation therapy was given but does not meet the criteria specified above, indicate why the criteria was not met. If the reason is not listed, report **Other** and specify the reason criteria were not met.

Questions 481 – 482: Year iron chelation therapy started

Indicate if the year iron chelation therapy was started is **Known** or **Unknown**. If **Known**, specify the year when iron chelation therapy began. If the start date of iron chelation therapy is not known, report **Unknown**.

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

Questions 483 – 484: Did the recipient have hepatomegaly? (> 2 cm below costal margin)

Indicate if the recipient had hepatomegaly (i.e. abnormal enlargement of the liver) at the last evaluation prior to the start of the preparative regimen / infusion. Hepatomegaly is often documented during the physician's physical assessment of the recipient and represents an abnormal finding. If **Yes**, report the liver measurement (in centimeters below the right costal margin).

If hepatomegaly was not present or is not known if it was present or absent at the last evaluation prior to the start of the preparative regimen, indicate **No** or **Unknown** and continue with question 471.

Questions 485 – 487: Was a liver biopsy performed at any time since diagnosis?

Evaluation of liver tissue may be necessary to determine the extent of the recipient's disease. Indicate if a liver biopsy was performed at any time since diagnosis.

If **Yes**, report if the assessment date was **Known** or **Unknown**. If **Known**, report the date of the liver biopsy. If multiple liver biopsies were performed since diagnosis, report the date of the most recent biopsy.

If the date of the liver biopsy is partially known, use the process described for reporting partial or unknown dates in General Instructions, Guidelines for Completing Forms; check the box **Date estimated**.

If a liver biopsy was not performed or it is unknown it a biopsy was performed at any time since diagnosis, report **No**.

Questions 488: Was there evidence of liver cirrhosis?

Indicate if the liver biopsy performed on the date reported above showed evidence of liver cirrhosis. Select **Yes** if the biopsy showed characteristics of liver cirrhosis were present.

Report **No** if the biopsy reported did not show characteristics of liver cirrhosis. If the results are unclear, seek physician clarification.

Select **Unknown** if no information is available to determine if the biopsy showed characteristics of liver cirrhosis.

Questions 489 – 490: Was there evidence of liver fibrosis?

Indicate if the liver biopsy performed on the date reported above showed evidence of liver fibrosis. Select **Yes** if the biopsy showed characteristics of liver fibrosis and specify the type of fibrosis observed.

- **Bridging:** Bands of fibrous tissue and collagen which span portal spaces and/or centrilobular spaces creating a “bridge-like” appearance
- **Periportal:** Fibrous expansion of portal fields with fibrosis extending along the terminal portal veins
- **Other:** Select this option if the type of fibrosis present is not listed.
- **Unknown:** Select this option if it if known fibrosis was present but the type is not known.

Report **No** if the biopsy did not show characteristics of liver fibrosis. If the results are unclear, seek physician clarification.

Select **Unknown** if no information is available to determine if the biopsy showed characteristics of liver fibrosis.

Questions 491: Was there evidence of chronic hepatitis?

Indicate if the liver biopsy performed on the date reported above showed evidence of chronic hepatitis. Select **Yes** if the biopsy showed characteristics of chronic hepatitis. Report **No** if the biopsy reported did not show characteristics of chronic hepatitis. If the results are unclear, seek physician clarification.

Select **Unknown** if no information is available to determine if the biopsy showed characteristics of chronic hepatitis or if the results were inconclusive.

Question 492: Was documentation submitted to the CIBMTR? (e.g., liver biopsy)

Indicate whether a liver biopsy is attached to support / clarify the center’s responses. For further instructions

on how to attach documents in FormsNet3^{SM}, refer to the Training Guide.

Question 493: Is there evidence of abnormal cardiac iron deposition based on an MRI of the heart at time of infusion?

A cardiac MRI may be performed to assess cardiac iron deposition. This information is typically listed within the MRI interpretation of the report.

Indicate **Yes** if cardiac MRI shows evidence of abnormal cardiac iron deposition at the time of infusion. Select **No** if there is no evidence of abnormal cardiac iron deposition at the time of infusion. If multiple MRIs were performed, report the results based on the most recent scan prior to the start of the preparative regimen / infusion.

Question 494: Did the recipient have a splenectomy at any time prior to infusion?

Indicate **Yes** or **No** if the recipient had a splenectomy at any time prior to the start of the preparative regimen / infusion. If it not known whether a splenectomy was performed at any time prior to the start of the preparative regimen / infusion, report **Unknown**.

Laboratory studies at last evaluation
Complete the serum iron, TIBC, and total serum bilirubin questions based on the most recent testing prior to the start of the preparative regimen / infusion. Tests can be performed on different days.

Questions 495 – 496: Serum iron

A serum iron test is used to determine how much iron is in the serum. If the serum iron level is lower than normal, it indicates the body's iron stores are low (iron deficiency). If the serum iron level is higher than normal, it could indicate hemochromatosis, a condition that causes the body to store too much iron.

Indicate whether the serum iron was **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion. If **Known**, report the value and unit of measure documented on the laboratory report.

Questions 497 – 498: Total iron binding capacity (TIBC)

Total iron binding capacity (TIBC) is a test used to gauge the total amount of iron in the blood.

Indicate whether the TIBC was **Known** or **Unknown** at the last evaluation prior to the start of the preparative regimen / infusion. If **Known**, report the value and unit of measure documented on the laboratory report

Questions 499 – 501: Total Serum bilirubin

Indicate whether the total serum bilirubin was **Known** or **Unknown** at the last evaluation prior to the start of

the preparative regimen / infusion. If **Known**, report the value, unit of measure, and specify the upper limit of normal for the total serum bilirubin documented on the laboratory report.

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
469	4/3/ 2024	Remove	Removed the red waring box above Q469, stating that Q469 – 501 only comes due for transfusion dependent thalassemia.	Due to change in FormsNet3 validations
494	10/25/ 2023	Add	Added clarification language to the blue box located below Q494: ***Laboratory studies at last evaluation*** *Complete the serum iron, TIBC, and total serum bilirubin questions based on the most recent testing prior to the start of the preparative regimen / infusion. Tests can be performed on different days*.	Added for clarification

Last modified: Apr 03, 2024

Q502 – 509: Disorders of Immune System

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of genetic / molecular / other blood testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Questions 502 – 505: 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**, **Other immunodeficiency** or **Other pigmentary dilution 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.

Question 506 – 507: Did the recipient have an active or recent infection with a viral pathogen within 60 days of HCT?

Viral infections are caused by exposure to a new virus or reactivation of a dormant virus already present in the body. The most common viral infections are due to HSV (Herpes Simplex Virus), and CMV (Cytomegalovirus). Report **Yes** if the recipient had an active or recent infection with a viral pathogen within 60 days of HCT and specify the viral pathogens causing the infection. Check all that apply.

If the recipient did not have an active or recent infection with a viral pathogen, report **No**.

Question 508: Has the recipient ever been infected with PCP/PJP:

PCP Pneumocystis is a common fungal infection commonly affecting the lungs. Indicate if the recipient has ever been infected with PCP/PJP.

Question 509: Does the recipient have GVHD due to maternal cell engraftment pre-HCT? (SCID only):

Recipients with SCID often have presence of maternal T lymphocytes (T cells) in the circulation. This is a complication that results from maternal-fetal transfusion and the failure in SCID patients to recognize and to reject foreign cells, allowing maternal T cells to engraft. This is also known as maternal engraftment. This engraftment can induce graft-versus-host disease (GVHD).

Report **Yes** if the recipient has a history of or current manifestations of GVHD due to maternal cell engraftment at the last evaluation prior to the preparative regimen and continue to signature line.

If the recipient does not have GVHD due to maternal cell engraftment pre-HCT, report **No** and submit the form.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Sep 23, 2022

Q510 – 511: Inherited Abnormalities of Platelets

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of genetic testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Questions 510 – 511: 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.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Sep 23, 2022

Q512 – 514: Inherited Disorders of Metabolism

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of genetic testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Questions 512 – 513: Specify inherited abnormalities of metabolism classification:

Indicate the inherited abnormalities of metabolism disease classification at diagnosis. If the subtype is not listed, report as Other inherited metabolic 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.

Question 514: Report the Loes composite score (Adrenoleukodystrophy (ALD) only):

The Loes composite score is often used to assess disease/progression for recipients with ALD. The Loes composite score is a rating from 0-34, this signifies the severity of abnormalities detected in the brain after evaluation of MRI. Report the Loes composite score. if the score is unknown, check with a transplant physician to determine this value.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Sep 23, 2022

Q515 – 519: Histocytic Disorders

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of molecular testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Questions 515 – 516: 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. If a certain disease becomes a common indication for HCT, the CIBMTR will add the disease as a separate category.

Question 517 – 518: Did the recipient have an active or recent infection with a viral pathogen within 60 days of HCT? Hemophagocytic lymphohistiocytosis (HLH) only:

Viral infections are caused by exposure to a new virus or reactivation of a dormant virus already present in the body. The most common viral infections are due to HSV (Herpes Simplex Virus), and CMV (Cytomegalovirus). Report **Yes** if the recipient had an active or recent infection with a viral pathogen within 60 days of HCT and specify the viral pathogen causing the infection. Check all that apply.

If the recipient did not have an active or recent infection with a viral pathogen, report **No**.

Question 519: Has the recipient ever been infected with PCP/PJP:

PCP Pneumocystis is a common fungal infection commonly affecting the lungs. Indicate if the recipient has ever been infected with PCP/PJP.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Sep 23, 2022

Q520 – 523: Autoimmune Diseases

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of molecular / autoimmune testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Questions 520 – 523: Specify autoimmune disease classification

Indicate the autoimmune disease classification at diagnosis. If the subtype is not listed, report as **Other autoimmune disease**, **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.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Sep 23, 2022

Q524 – 525: Tolerance Induction Associated with Solid Organ Transplant

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy). 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 exact diagnosis date is not known, use the process described in General Instructions, Guidelines for Completing Forms.

Questions 524 – 525: Specify transplanted organ: (check all that apply)

In an effort to achieve organ tolerance and potentially avoid long term systemic immunosuppression, a recipient may receive an infusion of cells prior to a subsequent solid organ transplant. Indicate the transplanted organ, if organ is not listed, report as **Other organ** and specify.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Sep 23, 2022

Q526: Other Disease

Question 1: Date of diagnosis of primary disease for HCT / cellular therapy

Report the date of the first pathological diagnosis (e.g., bone marrow or tissue biopsy) of the disease or the date of molecular / genetic testing. 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 diagnosed *in utero*, report the date of birth as the diagnosis date.

For any congenital diseases, the date of birth should be reported as the diagnosis date.

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

Question 526: 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. An example of another disease is dystrophic epidermolysis bullosa (DEB).

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Sep 23, 2022