2111: ALL Post-HCT

The Acute Lymphoblastic Leukemia Post-HCT Data Form is one of the Comprehensive Report Forms. This form captures ALL-specific post-HCT data such as: planned treatments post-HCT, the recipient's best response to HCT, disease relapse data including treatment administered for relapse or persistent disease, and disease status for the reporting period.

This form must be completed for all recipients randomized to the Comprehensive Report Form (CRF) track and whose primary disease is reported on Pre-TED Disease Classification Form (Form 2402), as Acute Lymphoblastic Leukemia (ALL). Recipients with precursor B-cell or precursor T-cell Lymphoblastic Lymphoma should be reported as precursor B-cell or precursor T-cell Acute Lymphoblastic Leukemia. The Acute Lymphoblastic Leukemia Post-HCT Data (Form 2111) must be completed in conjunction with each Post-HCT follow-up form (Forms 2100, 2200, and 2300) completed. The form is designed to capture specific data occurring within the timeframe of each reporting period (i.e., between day 0 and day 100 for Form 2100, between day 100 and the six-month date of contact for Form 2200, between the date of contact for the six-month follow up and the date of contact for the one-year follow up for Form 2200, etc.).

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.

Date	Manual Section	Add/ Remove/ Modify	Description
2/ 24/ 17	Comprehensive Disease-Specific Manuals	Modify	Updated explanations of triggers for disease inserts to refer to the primary disease reported on the Pre-TED Disease Classification Form (Form 2402) instead of the Pre-TED Form (Form 2400)
6/ 12/ 15	2111: ALL Post-HCT	Add	Added instruction for **METHOD** and **DATE** reporting in the Q73-96: Disease Status at the Time of Evaluation for This Reporting Period section. *See text for full detail.*

Q1-20: Disease Assessment at the Time of Best Response to HCT

Question 1: Compared to the disease status prior to the preparative regimen, what was the best response to HCT since the date of the last report? (Include response to any therapy given for post-HCT maintenance or consolidation, but exclude any response to therapy given for relapsed, persistent, or progressive disease)

Any specified therapy administered post-HCT to prolong remission or for minimal residual disease is considered part of the HCT and should be included when assessing the recipient's response to transplant.

Treatment given post-HCT for relapsed or persistent disease is not considered part of the HCT and should be excluded when assessing the response to HCT. If treatment was given post-HCT for relapsed or persistent disease, assess the patient's best response *prior* to the start of therapy. If therapy was only given for reasons other than relapsed or persistent disease, assess the patient's best response throughout the entire duration of the reporting period.

If the recipient was in remission at the start of the preparative regimen, indicate "continued complete remission" and continue with question 21.

Complete Remission (CR) criteria:
A treatment response where **all** of the following criteria are met 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., central nervous system or soft tissue involvement)
• ANC (absolute neutrophil count) of > 1,000/µL
• Platelets ≥ 100,000/µL
• Transfusion independent

Include recipients with persistent chromosomal or molecular abnormalities who otherwise meet all criteria of CR. If new chromosomal or molecular abnormalities (i.e., other than those present prior to the HCT) are evident post HCT, a physician must determine if they constitute cytogenetic or molecular relapse; the patient may still be in hematologic CR. Do not include recipients with extramedullary disease; they should be considered to have persistent disease or to be in relapse.

If a CR was achieved after transplant, check "complete remission" and continue with question 2.

If the recipient did not achieve CR prior to the start of the preparative regimen or following transplant, indicate “not in complete remission” and continue with question 21.

Question 2: Was the date of best response previously reported?

If the patient achieved complete remission in the current reporting period, indicate “no” and continue with question 3.

If the recipient achieved a complete remission during a previous reporting period, indicate “yes” and continue with question 21.

Question 3: Date assessed

Indicate the date hematologic CR was achieved. Report the date of the pathological evaluation (e.g., bone marrow biopsy) or blood/serum assessment (e.g., CBC, peripheral blood smear). Enter the date the sample was collected for pathological and laboratory evaluations.

Question 4: Was the disease status assessed by molecular testing (e.g., PCR)?

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

Indicate if molecular studies were obtained at the time the recipient achieved post-transplant CR.

If molecular studies were obtained, check “yes” and continue with question 5.

If molecular studies were not obtained, sample for molecular studies was inadequate, or it is unknown if molecular studies were performed, indicate “no” and continue with question 8.

Question 5: Date assessed

Report the date the sample was collected for molecular testing.

Question 6: Was disease detected?

Indicate if molecular studies showed abnormalities consistent with the recipient’s disease. If there are molecular abnormalities consistent with evidence of disease, check “yes” and continue with question 7.

If molecular study results were not consistent with evidence of disease, check “no” and continue with question 8.

Question 7: Was the status considered a disease relapse?

Indicate if the molecular abnormalities were considered to be relapsed disease. Criteria for molecular relapse are established by clinical judgment, and should reflect the clinical decision of the transplant physician. A recipient may be reported to have molecular relapse even in the setting of hematologic CR. Criteria for complete remission are based on hematologic and pathologic characteristics and are independent of molecular markers of disease.

If the recipient has molecular abnormalities that the physician considers to be consistent with molecular relapse, check “yes.” Also report relapse under the “Disease Relapse Post-HCT” section of this form.

If the recipient has molecular abnormalities that the physician does not consider to be consistent with molecular relapse, check “no.”

Question 8: Was the disease status assessed via flow cytometry?

Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tissue preparations for multiple unique cell characteristics. Its primary clinical purpose in the setting of leukemia 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.

Indicate if flow cytometry was performed on peripheral blood and/or bone marrow sample at the time the recipient achieved post-transplant CR.

If flow cytometry was performed, check “yes” and continue with question 9.

If flow cytometry was not performed, flow cytometry sample was inadequate, or it is unknown if flow cytometry was performed, indicate “no” and continue with question 12.

Question 9: Date assessed

Report the date the peripheral blood or bone marrow sample was collected for flow cytometry analysis.

Question 10: Was disease detected?

Indicate if evidence of disease was detected in the sample sent for flow cytometry analysis. Evidence of disease may include the presence of blasts or an immunophenotype known to characterize the patient’s

disease. If flow cytometry results were consistent with evidence of disease, check “yes” and continue with question 11.

If flow cytometry results were not consistent with evidence of disease, check “no” and continue with question 12.

Question 11: Was the status considered a disease relapse?

Indicate if the flow cytometry results were considered consistent with relapsed disease. Criteria for flow cytometric relapse are established by clinical judgment. Flow cytometry results showing ≥ 5% blasts are consistent with relapsed disease by hematologic remission criteria; additionally, an aberrant blast population of < 5% of the total cell population may be considered flow cytometric relapse in the absence of hematologic relapse. If the recipient has abnormalities by flow cytometry that the physician considers to be consistent with flow cytometric relapse, check “yes.” Also report relapse under the “Disease Relapse Post-HCT” section of this form.

If the recipient has residual disease by flow cytometry that the physician does not consider to be consistent with relapse, check “no.”

Question 12: Was the disease status assessed by cytogenetic testing (conventional or FISH)?

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

Indicate if cytogenetic studies were obtained at the time the recipient achieved post-transplant CR.

If cytogenetic studies were obtained, check “yes” and continue with question 13.

If no cytogenetic studies were obtained, cytogenetic samples were inadequate, or it is unknown if chromosome studies were performed, indicate “no” and continue with question 21.

Question 13: Was the disease status assessed via FISH?

FISH, fluorescence *in situ* hybridization, is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA commonly found in ALL. These probes are mixed with cells from the recipient’s blood. A fluorescent “tag” is then used to visualize the binding of the probe to the diseased cells.

FISH testing for sex chromosomes after sex-mismatched allogeneic HCT should not be considered disease assessment, as the purpose is to determine donor chimerism. Additionally, the FISH probe panel should reflect the patient's current disease; FISH may be used as surveillance for changes associated with post-therapy malignancy.

If FISH studies were obtained, check "yes" and continue with question 14.

If FISH studies were not obtained, FISH sample was inadequate, or it is unknown if FISH studies were performed, indicate "no" and continue with question 17.

Question 14: Date assessed

Report the date the sample was collected for FISH assessment.

Question 15: Was disease detected?

Indicate if evidence of disease was detected in the sample sent for FISH assessment. If FISH results were consistent with evidence of disease, check "yes" and continue with question 16.

If FISH results were not consistent with evidence of disease, check "no" and continue with question 17.

Question 16: Was the status considered a disease relapse?

Indicate if the FISH abnormalities were considered to be relapsed disease. Criteria for cytogenetic relapse are established by clinical judgment, and should reflect the clinical decision of the transplant physician. A recipient may be reported to have cytogenetic relapse even in the setting of hematologic CR. Criteria for complete remission are based on hematologic and pathologic characteristics and are independent of cytogenetic markers of disease.

If the recipient has FISH abnormalities that the physician considers to be consistent with cytogenetic relapse, check "yes." Also report relapse under the "Disease Relapse Post-HCT" section of this form.

If the recipient has FISH abnormalities that the physician does not consider to be consistent with cytogenetic relapse, check "no."

Question 17: Was the disease status assessed via conventional cytogenetics?

Conventional cytogenetics are 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. This is called karyotyping. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

If conventional cytogenetic studies were obtained, check “yes” and continue with question 18.

If conventional cytogenetic studies were not obtained, culture failed, or it is unknown if conventional cytogenetic studies were performed, indicate “no” and continue with question 21.

Question 18: Date assessed

Report the date the sample was collected for conventional cytogenetic assessment.

Question 19: Was disease detected?

Indicate if evidence of disease was detected in the sample sent for conventional cytogenetic assessment. If conventional cytogenetic results were consistent with evidence of disease, check “yes” and continue with question 20.

If conventional cytogenetic results were not consistent with evidence of disease, check “no” and continue with question 21.

Question 20: Was the status considered a disease relapse?

Indicate if the conventional cytogenetic abnormalities were considered to be relapsed disease. Criteria for cytogenetic relapse are established by clinical judgment, and should reflect the clinical decision of the transplant physician. A recipient may be reported to have cytogenetic relapse even in the setting of hematologic CR. Criteria for complete remission are based on hematologic and pathologic characteristics and are independent of cytogenetic markers of disease.

If the recipient has conventional cytogenetic abnormalities that the physician considers to be consistent with cytogenetic relapse, check “yes.” Also report relapse under the “Disease Relapse Post-HCT” section of this form.

If the recipient has conventional cytogenetic abnormalities that the physician does not consider to be consistent with cytogenetic relapse, check “no.”

Q21-37: Post-HCT Therapy

Question 21: Was therapy given since the date of the last report for reasons other than relapse or persistent disease? (Include any maintenance or consolidation therapy)

Indicate if the recipient received treatment for ALL during the current reporting period for any reason other than relapsed or persistent disease. If the patient received therapy for reasons other than relapsed or persistent disease, check “yes” and continue with question 22. If the patient did not receive therapy, or only received therapy for relapsed or persistent disease, check “no” and continue with question 38.

Question 22: Central nervous system irradiation

Radiation therapy uses high-energy ionizing radiation to “kill” malignant cells; however, much like non-targeted systemic therapy, radiation therapy does not specifically target malignant cells and has significant side effects. For that reason, high-dose radiation often targets a limited field. Indicate if the recipient received radiation therapy to their central nervous system (brain and/or spinal cord).

Question 23: Systemic therapy

Systemic therapy refers to a delivery mechanism where a therapeutic agent is delivered orally or intravenously, enters the bloodstream, and is distributed throughout the body. Intrathecal therapy administered via injection into the spinal subarachnoid space reaches the cerebral spinal fluid and acts on the central nervous system.

Indicate “yes” if the patient received systemic or intrathecal therapy and continue with question 24. If the patient did not receive systemic or intrathecal therapy, indicate “no” and continue with question 35.

Questions 24-34: Specify systemic or intrathecal therapy agents

Systemic therapy agents and treatment regimens vary based on disease, prognosis, and protocol. Drugs may be administered in an inpatient or outpatient setting, and treatment may consist of one or multiple drugs. Additionally, drugs may be administered on a single day, over consecutive days, or continuously.

Indicate “yes” or “no” for each drug administered for therapy during the current reporting period for reasons other than relapsed or persistent disease. Do not leave any responses blank. If the recipient received a chemotherapy agent that is not listed, check “yes” for “other systemic therapy” (question 33) and specify the treatment in question 34.

Question 35: Donor cellular infusions

A donor cellular infusion, or DCI, is a form of immunotherapy that is commonly used for a variety of purposes, including the treatment of refractory or recurrent disease. In the setting of refractory or recurrent disease, the DCI is used to create a graft-versus-leukemia/tumor (GVL/GVT) effect. In general, the recipient does not receive a preparative regimen prior to receiving the additional donor cells since replacement of the marrow is not the goal.

Indicate “yes” if the patient received one or more donor cellular infusion(s). If the patient did not receive a donor cellular infusion, check “no.”

Questions 36-37: Other therapy

If the patient received a therapy that is not listed, indicate “yes” and use question 37 to specify. If the patient did not receive a therapy that is not listed, check “no.”

Q38-72: Disease Relapse Post-HCT

Report if the recipient relapsed at any time during the reporting period by any method of assessment. Molecular and cytogenetic/FISH relapse may occur in the setting of hematologic remission.

Question 38: Was a disease relapse detected by molecular testing (e.g., PCR)?

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

If molecular studies were obtained and consistent with relapse at any point in the reporting period, check "yes" and continue with question 39.

If molecular studies were not consistent with relapse during the reporting period, indicate "no" and continue with question 40. Examples include no molecular studies obtained, sample for molecular studies was inadequate, it is unknown if molecular studies were performed, or molecular studies were obtained and were not consistent with relapse.

Question 39: Date assessed

Report the date the sample was collected for molecular testing.

Question 40: Was a disease relapse detected via flow cytometry?

Flow cytometry assessment is a method of analyzing peripheral blood, bone marrow, or tissue preparations for multiple unique cell characteristics. Its primary clinical purpose in the setting of leukemia 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 flow cytometry was performed and results were consistent with relapse at any point in the reporting period, check "yes" and continue with question 41.

If flow cytometry results were not consistent with relapse during the reporting period, indicate "no" and continue with question 42. Examples include: no flow cytometry assessment was performed, flow cytometry

sample was inadequate, it is unknown if flow cytometry was performed, or flow cytometry studies were obtained and were not consistent with relapse.

Question 41: Date assessed

Report the date peripheral blood or bone marrow sample was collected for flow cytometry analysis.

Question 42: Was a disease relapse detected by cytogenetic testing (conventional or FISH)?

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

If any cytogenetic studies were performed and results were consistent with relapse at any point in the reporting period, check "yes" and continue with question 43.

If cytogenetic studies were not consistent with relapse during the reporting period, indicate "no" and continue with question 47. Examples include: no karyotype or FISH studies performed, karyotype or FISH sample was inadequate, it is unknown if karyotype or FISH studies were performed, or karyotype or FISH studies were obtained and were not consistent with relapse.

Question 43: Was a disease relapse detected via FISH?

FISH, fluorescence *in situ* hybridization, is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA commonly found in ALL. These probes are mixed with cells from the recipient's blood. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

FISH testing for sex chromosomes after sex-mismatched allogeneic HCT should not be considered disease assessment, as the purpose is to determine donor chimerism. Additionally, the FISH probe panel should reflect the patient's current disease; FISH may be used as surveillance for changes associated with post-therapy malignancy.

If FISH studies were performed and consistent with relapse at any point in the reporting period, check "yes" and continue with question 44.

If FISH studies were not consistent with relapse during the reporting period, indicate "no" and continue with question 45. Examples include: no FISH studies performed, FISH sample was inadequate, it is unknown if FISH studies were performed, or FISH studies were obtained and were not consistent with relapse.

Question 44: Date assessed

Report the date the sample was collected for FISH assessment.

Question 45: Was a disease relapse detected via conventional cytogenetics?

Conventional cytogenetics are 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. This is called karyotyping. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

If conventional cytogenetic studies were performed and results were consistent with relapse at any point in the reporting period, check “yes” and continue with question 46.

If conventional cytogenetic studies were not consistent with relapse during the reporting period, indicate “no” and continue with question 47. Examples include: no conventional cytogenetics performed, conventional cytogenetic culture failed, it is unknown if conventional cytogenetic studies were performed, or conventional cytogenetics were obtained and were not consistent with relapse.

Question 46: Date assessed

Report the date the sample was collected for conventional cytogenetic assessment.

Question 47: Was a disease relapse detected by clinical/hematologic assessment?

Clinical and hematologic assessments are the least sensitive methods of establishing a patient’s disease status. Examples of 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.

If clinical and/or hematologic assessment was performed and consistent with relapse at any point in the reporting period, check “yes” and continue with question 48.

If clinical and/or hematologic assessment was not consistent with relapse, or if it is unknown if these assessments were performed, during the reporting period, indicate “no” and continue with question 73.

Question 48: Date assessed

Report the date of clinical or hematologic assessment. Enter the date the sample was collected for pathological and laboratory evaluations, the date the imaging took place for radiographic assessments, or the date the physical examination occurred.

Questions 49-54: Specify site(s) of disease relapse

Indicate “yes” or “no” for each site specified in questions 49-53. Do not leave any responses blank. Specify only sites of clinical or hematologic disease; cytogenetic and molecular evidence of disease does not need to be specified. If “yes” is indicated for “other site,” specify the site in question 54. At least one of questions 49-53 must be answered “yes.”

Question 55: Was any therapy given for relapsed disease since the date of the last report?

Indicate if the recipient received treatment for relapsed ALL during the current reporting period. Do not report therapy given for maintenance (to prolong remission or for minimal residual disease). If the patient received therapy for relapsed or persistent disease, check “yes” and continue with question 56. If the patient did not receive therapy, or only received therapy for maintenance or for minimal residual disease, check “no” and continue with question 73.

Question 56: Central nervous system irradiation

Radiation therapy uses high-energy ionizing radiation to “kill” malignant cells; however, much like non-targeted systemic therapy, radiation therapy does not specifically target malignant cells and has significant side effects. For that reason, high-dose radiation often targets a limited field. Indicate if the recipient received radiation therapy to their central nervous system (brain and/or spinal cord).

Question 57: Systemic therapy

Systemic therapy refers to a delivery mechanism where a therapeutic agent is delivered orally or intravenously, enters the bloodstream, and is distributed throughout the body. Intrathecal therapy administered via injection into the spinal subarachnoid space reaches the cerebral spinal fluid and acts on the central nervous system.

Indicate “yes” if the patient received systemic or intrathecal therapy and continue with question 58. If the patient did not receive systemic or intrathecal therapy, indicate “no” and continue with question 69.

Questions 58-68: Specify systemic or intrathecal therapy agents

Systemic therapy agents and treatment regimens vary based on disease, prognosis, and protocol. Drugs may be administered in an inpatient or outpatient setting, and treatment may consist of one or multiple drugs. Additionally, drugs may be administered on a single day, over consecutive days, or continuously.

Indicate “yes” or “no” for each drug administered for therapy during the current reporting period for reasons other than relapsed or persistent disease. Do not leave any responses blank. If the recipient received a chemotherapy agent that is not listed, check “yes” for “other systemic therapy” and specify the treatment in question 68.

Question 69: Donor cellular infusions

A donor cellular infusion, or DCI, is a form of immunotherapy that is commonly used for a variety of purposes, including the treatment of refractory or recurrent disease. In the setting of recurrent disease, the DCI is used to create a graft-versus-leukemia/tumor (GVL/GVT) effect. In general, the recipient does not receive a preparative regimen prior to receiving the additional donor cells since replacement of the marrow is not the goal.

Indicate "yes" if the patient received one or more donor cellular infusion(s). If the patient did not receive a donor cellular infusion, check "no."

Question 70: Subsequent HCT

HCT is defined as an infusion of a product that contains CD34+ cells (e.g., bone marrow, peripheral blood stem cells, cord blood, etc.). Refer to Appendix D for further clarification on defining a subsequent HCT.

The intention of an HCT is to restore hematopoiesis and immunity, and it is usually preceded by a preparative regimen used to both reduce disease burden and prevent rejection of the new stem cells by killing normal and malignant cells, if present. In some cases, a preparative regimen may not be used prior to the infusion of CD34+ cells, but this would still be considered an HCT.

If a recipient receives a subsequent HCT between the HCT follow-up time points (100 day, six months, annually), the comprehensive report form sequence will start over with another Pre-TED Form (2400), Recipient Baseline Data Form (2000), and Acute Myelogenous Leukemia Pre-HCT Data Form (2010). However, if the recipient receives an autologous HCT as a result of a poor graft or graft failure and if the previous HCT was also autologous, the comprehensive report form sequence **will not** start over. Generally this type of infusion (autologous rescue) is used to treat the recipient's poor graft response, rather than to treat the recipient's disease.

A subsequent HCT may be administered to replace or repopulate the recipient's marrow and reconstitute the immune system. If the recipient receives a subsequent HCT as treatment for relapsed disease, check "yes" and continue with question 71; only report a subsequent HCT given for relapsed disease.

Questions 71-72: Other therapy

If the patient received a therapy that is not listed, indicate "yes" and specify the therapy in question 72. If the patient did not receive a therapy not listed, check "no."

Q73-96: Disease Status at the Time of Evaluation for This Reporting Period

Disease Status at Time of Evaluation for this Reporting Period
Review the instruction below regarding method and date reporting for this section.

METHOD

This section should reflect the recipient's most recent disease assessment. Not all recipients have molecular, cytogenetic, FISH, and/or flow cytometric abnormalities identified to monitor disease status. If no disease assessments exist for the applicable method, check "no."

Molecular and cytogenetic assessments may be performed for many reasons post-transplant, including monitoring for secondary malignancy. If the recipient did not have any identified molecular, cytogenetic, FISH, or flow cytometric abnormalities at diagnosis or during their pre-transplant course, and post-HCT follow-up assessments continue to show that no abnormalities are detected, report "no" for these assessment data fields. However, if routine post-HCT molecular, cytogenetic, FISH, and/or flow cytometry assessments identify a new abnormality associated with the recipient's disease process, begin reporting those assessments; report the assessment identifying the new abnormality, as well as all subsequent assessments for the abnormality by that method.

If the recipient had molecular, cytogenetic, FISH, and/or flow cytometric abnormalities prior to transplant, ensure that post-HCT assessments of the applicable method are reported.

> **Example:** The recipient has TEL-AML1 abnormalities identified by PCR (molecular method) and FISH testing prior to transplant; however, they had a normal karyotype on all pre-transplant assessments. Post-transplant, TEL-AML1 molecular studies and FISH studies incorporating a TEL-AML1 probe should be reported; conventional cytogenetic studies would not be reported (answer question 88 as "no") unless the recipient develops abnormalities associated with their disease detectable by conventional cytogenetics; the study identifying the new abnormalities and all subsequent conventional cytogenetic studies would be reported.

DATE

If more than one test in the same assessment category is done on different days, report the date of the most definitive diagnostic assessment within a reasonable time frame of the date of contact (approximately 30 days). If there was only a single assessment performed within the reporting period, it should be reported, even if it was more than 30 days prior to the date of contact.

Example: Blasts appear in the peripheral blood on a CBC, the next day a bone marrow biopsy is done, also showing evidence of disease. Report the date of the bone marrow; it is the most recent and most definitive assessment.

Question 73: Was the disease status assessed since the date of the last report?

Molecular studies, flow cytometry, cytogenetic and FISH studies, and clinical/hematologic assessment are used to evaluate disease status. Indicate if the disease status was assessed using at least one of these methods at any time within the reporting period. In most cases if they were evaluated by a physician during the reporting period, the patient will have had at least a clinical and/or hematologic assessment. If no assessment was performed during the reporting period for which the form is being completed, continue with the signature section at the end of the form.

Question 74: Does the disease assessment reflect the relapsed disease in this reporting period (as captured in questions 38-54), without subsequent therapy?

This section of the form is intended to capture the most recent disease status assessment. If the recipient had a relapse reported on this form, with no subsequent therapy *and no subsequent disease assessment* in this reporting period, check "yes" and continue with question 95.

If the patient did not have a relapse, had relapse with subsequent therapy, or had a disease status evaluation nearer to the date of contact, indicate "no" and continue with question 75.

Example 1 (no relapse): If a disease assessment was performed within this form's reporting period and no relapse was reported for questions 38-54, "no" should be selected. The most recent disease assessments should be reported in questions 75-94.

Example 2 (relapsed and treated, but not reassessed): If a relapse was reported for questions 38-54, treatment was administered post relapse (reported in questions 55-72), but no new assessment was performed post treatment, "no" should be selected. There would be no disease assessments to report for questions 75-94.

Example 3 (relapsed, treated, and reassessed): If a relapse was reported for questions 38-54, treatment was administered post relapse (reported in questions 55-72), and a new assessment was performed post treatment, "no" should be selected and the most recent post-treatment assessments should be reported for questions 75-94.

Example 4 (untreated relapse): If the most recent disease status assessment is the same as that reflected in questions 38-54 and no additional treatment was administered since that assessment (question 55 answered "no"), check "yes" and continue with question 95.

Question 75: Was the disease status assessed by molecular testing (e.g., PCR)?

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

Molecular testing for chimerism after allogeneic HCT should not be considered disease assessment.

If molecular studies were obtained at any point in the reporting period, check "yes" and continue with question 76.

If molecular studies were not performed during the reporting period, indicate "no" and continue with question 79. Examples include: no molecular studies obtained, sample for molecular studies was inadequate, or it is unknown if molecular studies were performed.

Question 76: Date assessed

Report the date the sample was collected for molecular testing.

Question 77: Was disease detected?

Indicate if molecular studies showed abnormalities consistent with the recipient's disease. If there are molecular abnormalities consistent with evidence of disease, check "yes" and continue with question 78.

If molecular study results were not consistent with evidence of disease, check "no" and continue with question 79.

Question 78: Was the status considered a disease relapse?

Indicate if the molecular abnormalities were considered to be relapsed disease. Criteria for molecular relapse are established by clinical judgment, and should reflect the clinical decision of the transplant physician. If the recipient has molecular abnormalities that the physician considers to be consistent with molecular relapse, check "yes." Also report relapse under the "Disease Relapse Post-HCT" section of this form.

If the recipient has molecular abnormalities that the physician does not consider to be consistent with molecular relapse, check "no."

Question 79: Was the disease status assessed via flow cytometry?

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

If flow cytometry was performed at any point in the reporting period, check “yes” and continue with question 80.

If flow cytometry was not performed during the reporting period, indicate “no” and continue with question 83. Examples include: no flow cytometry was performed, sample for flow cytometry was inadequate, or it is unknown if flow cytometry was performed.

Question 80: Date assessed

Report the date the peripheral blood, bone marrow, or extramedullary specimen was collected for flow cytometry analysis.

Question 81: Was disease detected?

Indicate if evidence of disease was detected in the sample sent for flow cytometry analysis. Evidence of disease may include the presence of blasts or an immunophenotype known to characterize the patient’s disease. If flow cytometry results were consistent with evidence of disease, check “yes” and continue with question 82.

If flow cytometry results were not consistent with evidence of disease, check “no” and continue with question 83.

Question 82: Was the status considered a relapse?

Indicate if the flow cytometry results were considered to show relapsed disease. If the recipient’s flow cytometry results were considered to be consistent with relapse, check “yes.” Also report relapse under the “Disease Relapse Post-HCT” section of this form.

If the recipient has residual disease on the flow cytometry report that the physician does not consider to be consistent with relapse, check “no.”

Question 83: Was the disease status assessed by cytogenetic testing (conventional or FISH)?

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

If any cytogenetic studies were performed at any point in the reporting period, check "yes" and continue with question 84.

If cytogenetic studies were not performed during the reporting period, indicate "no" and continue with question 92. Examples include: no karyotype or FISH studies performed, karyotype or FISH sample was inadequate, or it is unknown if karyotype or FISH studies were performed.

Question 84: Was the disease status assessed via FISH?

FISH, fluorescence *in situ* hybridization, is a sensitive technique that assesses a large number of cells. This technique uses special probes that recognize and bind to fragments of DNA commonly found in ALL. These probes are mixed with cells from the recipient's blood. A fluorescent "tag" is then used to visualize the binding of the probe to the diseased cells.

FISH testing for sex chromosomes after sex-mismatched allogeneic HCT should not be considered disease assessment, as the purpose is to determine donor chimerism. Additionally, the FISH probe panel should reflect the patient's current disease; FISH may be used as surveillance for changes associated with post-therapy malignancy.

If FISH studies were performed at any point in the reporting period, check "yes" and continue with question 85.

If FISH studies were not performed during the reporting period, indicate "no" and continue with question 88. Examples include: no FISH studies performed, FISH sample was inadequate, or it is unknown if FISH studies were performed.

Question 85: Date assessed

Report the date the sample was collected for FISH assessment.

Question 86: Was disease detected?

Indicate if evidence of disease was detected in the sample sent for FISH assessment. If FISH results were consistent with evidence of disease, check "yes" and continue with question 87.

If FISH results were not consistent with evidence of disease, check “no” and continue with question 88.

Question 87: Was the status considered a relapse?

Indicate if the FISH assessment was considered to show relapsed disease. If the recipient’s FISH results were considered to be consistent with relapse, check “yes.” Also report relapse under the “Disease Relapse Post-HCT” section of this form.

If the recipient has abnormalities on FISH assessment that the physician does not consider to be consistent with relapse, check “no.”

Question 88: Was the disease status assessed via conventional cytogenetics?

Conventional cytogenetics are 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. This is called karyotyping. Banding pattern differentiation and chromosomal reconfiguration demonstrate evidence of disease.

If conventional cytogenetic studies were performed at any point in the reporting period, check “yes” and continue with question 89.

If conventional cytogenetic studies were not performed during the reporting period, indicate “no” and continue with question 92. Examples include: no conventional cytogenetics performed, conventional cytogenetic culture failed, or it is unknown if conventional cytogenetic studies were performed.

Question 89: Date assessed

Report the date the sample was collected for conventional cytogenetic assessment.

Question 90: Was disease detected?

Indicate if evidence of disease was detected in the sample sent for conventional cytogenetic assessment. If conventional cytogenetic results were consistent with evidence of disease, check “yes” and continue with question 91.

If conventional cytogenetic results were not consistent with evidence of disease, check “no” and continue with question 92.

Question 91: Was the status considered a relapse?

Indicate if the conventional cytogenetic assessment was considered to show relapsed disease. If the recipient's karyotype results were considered to be consistent with relapse, check "yes." Also report relapse under the "Disease Relapse Post-HCT" section of this form.

If the recipient has abnormalities on conventional cytogenetic assessment that the physician does not consider to be consistent with relapse, check "no."

Question 92: Was the disease status assessed by clinical/hematologic assessment?

Clinical and hematologic assessments are the least sensitive methods of establishing a patient's disease status. 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.

If clinical and/or hematologic assessment was performed at any point in the reporting period, check "yes" and continue with question 93.

If no clinical and/or hematologic assessment was performed, or if it is unknown if they were done during the reporting period, indicate "no" and continue with question 95.

Question 93: Date assessed

Report the date of clinical or hematologic assessment. The date reported should be that of the most disease-specific assessment within a reasonable timeframe of the date of contact (approximately 30 days). Enter the date the sample was collected for pathological and laboratory evaluations, the date the imaging took place for radiographic assessments, or the date of physical examination.

Question 94: Was disease detected?

Indicate if evidence of disease was detected by clinical and/or hematologic assessment. If clinical and/or hematologic assessment is consistent with evidence of disease, check "yes" and continue with question 95.

If clinical and/or hematologic assessment is not consistent with evidence of disease, check "no" and continue with question 95.

Question 95: What is the current disease status?

Indicate the disease status of ALL as of the last evaluation during the reporting period.

Hematologic complete remission (CR) must meet **all** of the following 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., central nervous system or soft tissue involvement)
- ANC of > 1,000/µL
- Platelets ≥ 100,000/µL
- Transfusion independent

Include recipients with chromosomal or molecular abnormalities who otherwise meet all criteria of CR. Additionally, some clinical judgment is required for evaluating whether a recipient meets the CR criteria, specifically neutrophil, platelet, and transfusion parameters. If a recipient does not meet these specifications, the underlying cause should be assessed; if the cause for not meeting one of these parameters is felt to be due to a reason other than underlying leukemia, such as renal insufficiency, hemolysis, infection, or drug-related causes, the disease status may be reporting as "complete remission." If the cause for not meeting the parameters is judged to be leukemia-related, the disease status should be reported as "not in complete remission."

If the recipient is in hematologic complete remission, check "complete remission." If the recipient did not achieve CR, indicate "not in complete remission."

Question 96: Date assessed

Enter the date of the most recent assessment establishing disease status within the reporting period. The date reported should be that of the most disease-specific assessment within a reasonable timeframe of the date of contact (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, the date the imaging took place for radiographic assessments, or the date of physical examination.

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