CIBMTR® CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Instructions for Hemophagocytic Lymphohistiocytosis Post-HCT Data (Form 2139)

This section of the CIBMTR Forms Instruction Manual is intended to be a resource for completing the Hemophagocytic Lymphohistiocytosis Form.

E-mail comments regarding the content of the CIBMTR Forms Instruction Manual to: CIBMTRFormsManualComments@nmdp.org. Comments will be considered for future manual updates and revisions. For questions that require an immediate response, please contact your transplant center's CIBMTR CRC.

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Hemophagocytic Lymphohistiocytosis Post-HCT Data

Hemophagocytic Lymphohistiocytosis (HLH) is a rare condition characterized by immune dysregulation, which generally manifests as an exaggerated immune response to a trigger (such as infection). Based on genetics and family history, the disease is divided into "primary" and "secondary" HLH. Those with a genetic component or clear family history are classified as "primary" and have "familial hemophagocytic lymphohistiocytosis" (FHL). Subtypes of FHL are numbered one through five. They are often diagnosed in infancy with molecular, hematologic, and clinical assessments. Those who are diagnosed as older children or adults have "secondary" HLH and may not have a genetic component or family history of the disease. HLH may be triggered by an infection, malignancy, or other autoimmune condition. Manifestations of HLH include prolonged fever, hepatosplenomegaly, bleeding, skin rash, central nervous system (CNS) abnormalities (such as seizures), jaundice, cytopenia(s), coagulopathy, hyperlipidemia, hypofibrinogenemia, hyperferritinemia, transaminitis, hyperbilirubinemia, hypoalbuminemia, and hyponatremia.

The Hemophagocytic Lymphohistiocytosis Post-HCT Data Form is one of the Comprehensive Report Forms. This form captures HLH-specific Post-HCT data such as the disease assessment since the date of the last report.

This form must be completed for all recipients randomized to the Comprehensive Report Form (CRF) track whose primary disease is reported on form 2400, question 357 as "histiocytic disorders" and question 635 as "hemophagocytic lymphohistiocytosis (HLH)." The HLH Post-HCT Data (Form 2118) 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 six-month follow-up Form 2200; and between the date of contact for the six-month follow-up Form 2200 and the date of contact for the one-year follow-up Form 2200, etc.).

Key Fields

Accuracy of the Key Fields is essential for ensuring that:

- Data are being reported for the correct recipient.

- Outcomes data accurately reflects appropriate transplant type and product for each transplant center.

- Data are being shared with the correct donor center, cord blood bank, cooperative registry, or other agency.

The Key Fields precede the form body and are automatically populated in the FormsNet3^{SM} application based on information provided on the CRID Assignment Form 2804. If errors are noted in the key fields, correct Form 2804 and then review it for accuracy. After Form 2804 has been corrected, verify data has been updated on all completed forms. If the data has not been updated automatically, centers will need to reprocess the completed forms to correct the key field data. If errors are noted in key fields for second or subsequent transplants, contact your CRC to make any necessary corrections to the transplant or product type. Transplant and product type will not be automatically populated on product or donor specific forms (Forms 2004, 2005, and 2006) and will need to be manually reported.

Disease Assessment Since the Date of Last Report

Indicate which of the following clinical features and laboratory findings were present on the **most recent evaluation since the date of the last report**. For values assessed multiple times since the date of the last report, report the most recent results.

Question 1: Anemia (Hgb < 9 g/dL):
Indicate if the recipient had anemia on the most recent evaluation since the date of the last report. Anemia is defined as hemoglobin less than 9 g/dL. Select "yes," "no," or "unknown."

Question 2: Degranulation assay of NK cells:
Degranulation in natural killer (NK) cells is the process by which NK cells release granules containing chemicals (perforin and granzymes) that are used to destroy targeted cells. In some subtypes of FHL (FHL3, 4, and 5), degranulation of NK cells is absent or abnormally low. A granule release assay (GRA) can be used to assess the degranulation indirectly by measuring the expression of CD107a on the cell surface following stimulation. This expression is only detectable when the granules fuse with the cell membrane, thus the absence of CD107a by GRA would indicate a defect in some part of NK degranulation. Indicate if the degranulation assay of NK cells was "normal," "abnormal," or "unknown" on the most recent evaluation since the date of the last report.

Question 3: Fever:
Indicate if the recipient had fever on the most recent evaluation since the date of the last report. Fever is defined as a temperature above 38.5° C (>101.3° F) for more than 7 days. Select "yes," "no," or "unknown."

Question 4: Hepatomegaly (liver edge palpable > 3 cm below right costal margin)
Indicate if the recipient had hepatomegaly (enlargement of the liver) on the most recent evaluation since the date of the last report. Hepatomegaly is defined by the palpability of the liver edge 3 cm or more below the right costal margin. Indicate "yes," "no," or "unknown."

Questions 5-6: Serum ferritin:
Indicate if the serum ferritin level was tested since the date of the last report. If "known," indicate the most recent value in question 6. If "unknown," continue with question 7.

Questions 7-8: Triglycerides:
Indicate if the triglyceride level was tested since the date of the last report. If "known," indicate the most recent value in question 8. If "unknown," continue with question 9.

Questions 9-10: Fibrinogen antigen assay (factor I; fibrinogen activity; functional fibrinogen; fibrinogen antigen):
Fibrinogen levels may be low in patients with HLH. Indicate if a fibrinogen antigen assay (factor 1; fibrinogen activity; functional fibrinogen; fibrinogen antigen) level was tested since the date of the last report. If "known," indicate the most recent value (and corresponding unit) in question 10. If "unknown," continue with question 11.

Question 11: NK cell function:
NK cell function is measured by a cytotoxicity assay.

NK cell function may be absent or reduced in those with HLH. Indicate the NK cell function on the most recent evaluation since the date of the last report; select "absent (≤ 10% lower limit of normal)," "decreased (11-50% lower limit of normal)," "normal," or "unknown."

Question 12: Neutropenia (ANC < 1.0 x 10^9/L):
Indicate if the recipient was neutropenic on the most recent evaluation since the date of the last report. Neutropenia is defined as an absolute neutrophil count (ANC) less than 1.0 x 10^9/L. Indicate "yes," "no," or "unknown."

Question 13: Soluble interleukin-2 receptor alpha chain (sCD25): (As defined by local laboratory)
Indicate the soluble interleukin-2 receptor alpha chain (soluble IL-2R, sCD25) level on the most recent evaluation since the date of the last report. The results of the test should be reported as defined by the local laboratory. Indicate if the soluble IL-2R alpha chain level was "normal," "elevated," or "unknown."

Question 14: Splenomegaly (spleen palpable > 3 cm below left costal margin):
Indicate if the recipient had splenomegaly (enlargement of the spleen) on the most recent evaluation since the date of the last report. Splenomegaly is defined by the palpability of the spleen edge 3 cm or more below the left costal margin. Indicate "yes," "no," or "unknown."

Question 15: Thrombocytopenia (platelets < 100 x 10^9/L):
Indicate if the recipient was thrombocytopenic on the most recent evaluation since the date of the last report. Thrombocytopenia is defined as a platelet count less than 100 x 10^9/L. Indicate "yes," "no," or "unknown."

Question 16: Neopterin level:
The measurement of neopterin in the cerebrospinal fluid (CSF) is useful to determine immune system activity. Indicate the neopterin level in the CSF on the most recent evaluation since the date of the last report. Indicate "normal" or "elevated." "Elevated" indicates levels above the upper limit of normal for the laboratory processing the specimen. If an assessment of neopterin levels in the CSF was not done since the date of the last report, select "not done."

Question 17: Protein:
Indicate the protein level in the cerebrospinal fluid (CSF) on the most recent evaluation since the date of the last report. Indicate "normal" or "elevated." "Elevated" indicates levels above the upper limit of normal for the laboratory processing the specimen. If an assessment of protein levels in the CSF was not done since the date of the last report, select "not done."

Question 18: WBC count:
Indicate the WBC count in the cerebrospinal fluid (CSF) on the most recent evaluation since the date of the last report. Indicate "normal" if there were less than or equal to 5 cells/µL in the CSF. Indicate "elevated" if there were greater than 5 cells/µL in the CSF. If an assessment of WBC count in the CSF was not done since the date of last report, select "not done."

Question 19: Were central nervous system (CNS) abnormalities found on a computed tomography (CT or CAT) or magnetic resonance imaging (MRI) scan since the date of the last report?

Indicate if radiology (CT, CAT, and/or MRI) performed on the recipient since the date of the last report detected any abnormalities in the CNS. CNS abnormalities may include lesions, leptomeningeal enhancements, or edema.

If CNS abnormalities were detected on the radiological examination at the most recent evaluation since the date of the last report, select "yes" and continue with question 20. If no CNS abnormalities were detected on the radiological examination, select "no" and continue with question 21. If it is unknown if abnormalities were present or if no CT/CAT/MRIs were performed, select "unknown" and continue with question 21.

Question 20: Was documentation submitted to the CIBMTR?

Indicate if a copy of the CNS radiography results is attached. Use the Log of Appended Documents (Form 2800) to attach a copy. Attaching a copy of the report may prevent additional queries.

Question 21: Did any clinical neurologic abnormalities persist or develop?

Based on a clinical neurologic assessment, indicate if there were any clinical neurological abnormalities that persisted or developed since the date of the last report. Neurologic abnormalities include abnormal gait, cranial nerve palsies, developmental delay, motor weakness, seizures, and sensory deficits. If clinical neurological abnormalities were present on the most recent evaluation since the date of the last report, select "yes" and continue with question 22. If no clinical neurologic abnormalities were present, select "no" and continue with question 30. If it is unknown if a clinical neurological exam was performed or if the results of the exam are not known, select "unknown" and continue with question 30.

Questions 22-29: Specify neurologic abnormalities:

Indicate the clinical neurologic abnormalities identified since the date of last report. Select "yes" or "no" for each question, ensuring that no question is left blank. If a neurological abnormality is not listed but was present, select "yes" for question 28 ("Other neurologic abnormality") and use question 29 to specify the abnormality.

Question 30: Were there any signs of disease relapse/reactivation?

Indicate if there were any signs of new or recurrent disease since the date of the last report. These signs may be present in the central nervous system and detected on radiology (CT/MRI) or clinical neurologic exam, **or** based on systemic disease assessments. If there were any signs of disease relapse or reactivation since the date of the last report, select "yes" and continue with question 31. If there was no evidence of disease relapse or reactivation since the date of the last report, select "no" and continue with the signature lines.

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Question 31: Specify the date of the relapse/reactivation:
Indicate the date that relapse or reactivation was detected. Use the date of the radiological exam, the date of the clinical neurologic exam, or the date the sample was collected for systemic disease assessment when relapse/reactive was determined.

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 32: Specify the site of the relapse/reactivation:
Indicate if the site of relapse or reactivation was CNS, systemic, or CNS <u>and</u> systemic. CNS disease is limited to findings in the central nervous system by radiology (CT or MRI) or features specific to the CNS in the clinical neurologic exam. Systemic disease includes findings in the blood counts, triglycerides, ferritin, fibrinogen, and/or hepatosplenomegaly evaluations.

Signature Lines:
The FormsNet3^{SM} application will automatically populate the signature data fields, including name and email address of person completing the form and date upon submission of the form.