



## Instructions for Hemophagocytic Lymphohistiocytosis Pre-HCT Data (Form 2039)

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](mailto: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 Pre-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 Pre-HCT Data Form is one of the Comprehensive Report Forms. This form captures HLH-specific Pre-HCT data such as the disease assessment, clinical and laboratory features at diagnosis, history of infection, pre-transplant therapy, and clinical and laboratory studies prior to the start of the preparative regimen.

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).”

Weitzman S. Difficult Pediatric Consultations: Consultative Hematology II “Approach to Hemophagocytic Disorders.” *ASH Education Book*. 2011;2011(1):178-83.

Gholam C, Grigoriadou S, Gilmour KC, Gaspar HB. Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. *Clin Exp Immunol*. 2011;163(3):271-83.

## 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<sup>SM</sup> 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.

## Subsequent Transplant

**Is this the report of a second or subsequent transplant for the same disease?**

If this is a second or subsequent transplant for hemophagocytic lymphohistiocytosis (HLH), indicate “yes” and continue with question 108. Indicating “yes” allows the

diagnosis and previous treatment sections of the form to be skipped, as they have already been collected on the baseline form for the first transplant.

If this is a report of a second or subsequent transplant for the same disease subtype and **this baseline disease insert was not completed for the previous transplant** (e.g., patient was on TED track for the prior HCT or prior HCT was autologous with no consent), select “no” and begin at question 1.

If this is a report of a second or subsequent transplant for a different disease (or a baseline form for HLH was not completed for the reasons suggested above), select “no” and begin the form at question 1.

## Disease Assessment at Diagnosis

### Question 1: Is this recipient a registered participant in the United States Immunodeficiency Network (USIDNET)?

The United States Immunodeficiency Network (USIDNET) is a research consortium studying primary immune deficiencies. They maintain a registry of primary immunodeficiency patients and act as a resource for clinical and laboratory research. Indicate if the recipient is a registered participant in the USIDNET. If “yes,” continue with question 2. If “no,” continue with question 3.

### Question 2: USIDNET ID:

Report the recipient’s USIDNET participant identification number.

### Question 3: What was the date of diagnosis?

Diagnosis is based on molecular OR diagnostic criteria below:

Molecular Diagnosis	Diagnostic Criteria
<p>A molecular diagnosis consistent with HLH:</p> <p><i>PRF1</i> <i>UNC13D(MUNC13-4)</i> <i>STX11</i> <i>STXBP2</i> <i>BIRC4</i> <i>ITK</i></p>	<p>Meets diagnostic criteria for HLH (5 of 8 criteria below)</p> <ul style="list-style-type: none"> <li>• Fever</li> <li>• Splenomegaly</li> <li>• Cytopenias (affecting ≥ 2 of 3 lineages in the peripheral blood)                             <ul style="list-style-type: none"> <li>– Hemoglobin &lt; 90 g/L (9.0 g/dL) (in infants &lt; 4 weeks: hemoglobin &lt; 100g/L (10.0 g/dl)</li> <li>– Platelets &lt; 100 x 10<sup>9</sup>/L</li> <li>– Absolute neutrophil count &lt; 1.0 x 10<sup>9</sup>/L</li> </ul> </li> <li>• Hypertriglyceridemia and/or hypofibrinogenemia:                             <ul style="list-style-type: none"> <li>– Fasting triglycerides ≥ 3.0 mmol/L (265 mg/dL)</li> <li>– Fibrinogen ≤ 1.5 g/L</li> </ul> </li> <li>• Hemophagocytosis in bone marrow, spleen, or lymph nodes</li> <li>• Low or absent NK-cell activity (according to local laboratory reference)</li> <li>• Ferritin ≥ 500 µg/L</li> <li>• Soluble CD25 (soluble IL-2 receptor) ≥ 2,400 U/mL</li> </ul>

or

Adapted from:

Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. V 2007;48(2):124-31.

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Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-52.

HLH is characterized by multiple clinical, laboratory, and genetic features, rather than distinct pathological characteristics. Examples of testing done to confirm a diagnosis of HLH include molecular analysis to determine defects in *PRF1*, *UNC13D*, *STX11*, *STXBP2*, and *ITK* genes. In situations where molecular testing did not result in diagnosis, the date of diagnosis should be the date the sample was collected for the last assessment used to establish a diagnosis of HLH (i.e., the 5<sup>th</sup> criteria that establishes 5 of 8 diagnostic criteria are met, in the absence of molecular marker). If there is a strong family history of HLH and no testing was done to confirm the diagnosis, report the recipient's date of birth as the date of diagnosis.

**Questions 4-10: Is there a family history of hemophagocytic disorders?**

Indicate if there is a family history of hemophagocytic disorders. Family history includes the recipient's biological aunts, uncles, cousins, and/or siblings. If there is a family history of hemophagocytic disorders, indicate "yes" and continue with questions 5-10. In questions 5-9, indicate the biological family member(s) that were affected by the hemophagocytic disorder. Indicate "yes" or "no" for each member listed, leaving no question blank. If a biological family relationship is not listed, select "other family member" in question 9 and specify the relationship in question 10.

If there is no family history of hemophagocytic disorders, select "no" and continue with question 11. If it is unknown if there is a family history of hemophagocytic disorders, indicate "unknown" and continue with question 11.

**Question 11: Is there a family history of consanguinity (inter-familial marriage/descent from common ancestors)?**

Consanguinity describes a relationship between people who share common ancestors (i.e., are "blood-relatives"). Indicate if there is a family history of consanguinity in the direct ancestry of the recipient. This includes the recipient's parents, grandparents, great-grandparents, etc. Indicate "yes" if there is a known history of consanguinity. Indicate "no" if there is no family history of consanguinity. Indicate "unknown" if the family history is not known.

**Question 12: Was genetic testing used to confirm the diagnosis?**

Genetic testing includes molecular methods to detect mutations characteristic of the disease. Genetic mutations for HLH include Perforin deficiency (*PRF1*) MUNC 13-4 (*UNC13D*), Syntaxin 11 (*STX11*), Munc 13-2 (*STXBP2*), and IL-2 inducible T-cell kinase (*ITK*). Indicate if genetic testing was performed to confirm the diagnosis. If "yes," continue with question 13. If "no," continue with question 20. If it is unknown if genetic testing was performed to confirm the diagnosis, indicate "unknown" and continue with question 20.

**Questions 13-19: Specify genetic mutation(s) identified:**

For each genetic mutation listed, indicate if the mutation was identified. If the genetic test was performed and the mutation was present, indicate “Yes.” If the genetic analysis was performed, but the mutation was absent, indicate “No.” If it is unknown if the test for the genetic mutation was performed or if the results are unknown, indicate “unknown.” If the test was not done for the genetic mutation, select “not done.” Do not leave any of the questions blank. If a test for a different mutation was performed, indicate the results of the test in question 18 and specify the other mutation in question 19. If no testing was done for mutations other than those already listed, select “not done” for question 18.

**Question 20: Were central nervous system (CNS) abnormalities found on computed tomography (CT or CAT) or magnetic resonance imaging (MRI) scans?**

Indicate if radiology (CT, CAT, and/or MRI) performed on the recipient detected any abnormalities in the central nervous system (brain and spinal cord) at the time of diagnosis. CNS abnormalities may include lesions, leptomeningeal enhancements, or edema.

If the recipient did have CNS abnormalities found on imaging at diagnosis, select “yes” and continue with question 21. If the recipient did not have CNS abnormalities detected by imaging, select “no” and continue with question 23. If it is unknown if the recipient had imaging done or if the results of imaging studies are not known, select “unknown” and continue with question 23.

<sup>†</sup>Jordan MB, Allen CE, Weitzman S, Filipovich AH, McClain KL. How I treat hemophagocytic lymphohistiocytosis. *Blood*. 2011;118(15):4041-52.

**Question 21: Date scan was performed:**

Enter the date the radiological assessment was performed.

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 22: Was documentation submitted to the CIBMTR?**

Indicate if a copy of the CT, CAT, or MRI scan(s) is attached. Use the Log of Appended Documents (Form 2800) to attach a copy of CT, CAT, or MRI report(s). Attaching a copy of the report may prevent additional queries.

## Clinical Features and Laboratory Studies at Diagnosis

Report findings prior to any treatment of the primary disease for which the HCT is being performed.

**Question 23: Anemia (Hgb < 9 g/dL):**

Indicate if the recipient had anemia at diagnosis or prior to the start of treatment for HLH. Anemia is defined as hemoglobin less than 9 g/dL. Select “yes,” “no,” or “unknown.”

**Question 24: Degranulation assay of NK cells (as defined by local laboratory):**

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 results of the degranulation assay of NK cells were “normal,” “abnormal,” or “unknown” at diagnosis.

\*Gholam C, Grigoriadou S, Gilmour KC, Gaspar HB. Familial haemophagocytic lymphohistiocytosis: advances in the genetic basis, diagnosis and management. *Clin Exp Immunol.* 2011;163(3):271-83.

**Question 25: Fever (> 38.5° C or > 101.3° F for > 7 days within 1 week of diagnosis):**

Indicate if the recipient had fever at diagnosis for HLH. The fever should last more than 7 days and be within 1 week of diagnosis. Fever is defined as a temperature above 38.5° C (101.3° F) for more than 7 days within 1 week of diagnosis. Select “yes,” “no,” or “unknown.”

**Question 26: Hepatomegaly (liver edge palpable > 3 cm below right costal margin):**

Indicate if the recipient had hepatomegaly (enlargement of the liver) at diagnosis or prior to the start of treatment for HLH. 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 27-28: Serum ferritin:**

Indicate if the serum ferritin level was known at diagnosis or prior to the start of treatment for HLH. If “known,” indicate the value in question 28. If “unknown,” continue with question 29.

**Questions 29-30: Triglycerides:**

Indicate if the triglyceride level was known at diagnosis or prior to the start of treatment for HLH. If “known,” indicate the value in question 30. If “unknown,” continue with question 31.

**Questions 31-32: 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 known at diagnosis or prior to the start of treatment for HLH. If “known,” indicate the value (and corresponding unit) in question 32. If “unknown,” continue with question 33.

**Question 33: NK cell function:**

NK cell function is measured by a cytotoxicity assay.

NK cell function (cytotoxicity) may be absent or reduced in those with HLH. Indicate the NK cell function at diagnosis or prior to the start of treatment for HLH; select “absent ( $\leq 10\%$  lower limit of normal),” “decreased (11-50% lower limit of normal),” “normal,” or “unknown.”

**Question 34: Neutropenia (ANC <  $1.0 \times 10^9/L$ ):**

Indicate if the recipient was neutropenic at diagnosis or prior to the start of therapy for HLH. Neutropenia is defined as an absolute neutrophil count (ANC) less than  $1.0 \times 10^9/L$ . Indicate “yes,” “no,” or “unknown.”

**Question 35: Soluble interleukin-2 receptor alpha chain (sCD25): (As defined by local laboratory)**

The presence of soluble interleukin-2 receptors (soluble IL-2R, sCD25) in the plasma indicates the activation of T cells. Elevated soluble IL-2R is indicative of prolonged T-cell activation, indicating a protracted immune response. Levels of soluble IL-2R differ based on age, so using age-based reference ranges is helpful to identify abnormal results\* Indicate the soluble IL-2R alpha chain level at diagnosis or prior to the start of therapy for HLH. 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.”

\*Zhang K, Filipovich AH, Johnson J, et al. Hemophagocytic Lymphohistiocytosis, Familial. 2006 Mar 22 [Updated 2013 Jan 17]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013. Accessed at: <http://www.ncbi.nlm.nih.gov/books/NBK1444/> on October 3, 2013.

**Question 36: Splenomegaly (spleen palpable > 3 cm below left costal margin):**

Indicate if the recipient had splenomegaly (enlargement of the spleen) at diagnosis or prior to the start of treatment for HLH. 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 37: Thrombocytopenia (platelets <  $100 \times 10^9/L$ ):**

Indicate if the recipient was thrombocytopenic at diagnosis or prior to the start of therapy for HLH. Thrombocytopenia is defined as a platelet count less than  $100 \times 10^9/L$ . Indicate “yes,” “no,” or “unknown.”

**Question 38: 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 at diagnosis or prior to the start of therapy for HLH. 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 at diagnosis or prior to the start of therapy for HLH, select “not done.”

**Question 39: Protein:**

Indicate the protein level in the cerebrospinal fluid (CSF) at diagnosis or prior to the start of therapy for HLH. 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 at diagnosis or prior to the start of therapy for HLH, select “not done.”

**Question 40: WBC count:**

Indicate the WBC count in the cerebrospinal fluid (CSF) at diagnosis or prior to the start of therapy for HLH. Indicate “normal” if there were less than or equal to 5 cells/ $\mu$ L in the CSF. Indicate “elevated” if there were greater than 5 cells/ $\mu$ L in the CSF. If an assessment of WBC count in the CSF was not done at diagnosis or prior to the start of therapy for HLH, select “not done.”

**Questions 41-47: Specify the site(s) where hemophagocytosis was documented at diagnosis:**

Indicate the site(s) where hemophagocytosis was present at diagnosis or prior to the start of any therapy for HLH. Hemophagocytosis is the process in which a phagocyte engulfs red blood cells, white blood cells, or platelets. Hemophagocytosis is a characteristic of HLH, but does not need to be present for diagnosis; it is one of eight criteria of which five must be met. Select “yes” or “no” for each question, ensure that no question is left blank. If a site is not listed but hemophagocytosis was present, select “yes” for question 46 (“other site”) and specify the site using question 47.

## **Disease Assessment Between Diagnosis and the Start of the Preparative Regimen**

**Question 48: Were central nervous system (CNS) abnormalities found on computed topography (CT or CAT) or magnetic resonance imaging (MRI) scans?**

Indicate if radiology (CT, CAT, and/or MRI) performed on the recipient between diagnosis and the start of the preparative regimen detected any abnormalities in the CNS (brain and spinal cord). CNS abnormalities may include lesions, leptomeningeal enhancements, or edema.

If CNS abnormalities were detected on the radiological examination, select “yes” and continue with question 49. If no CNS abnormalities were detected on the radiological examination, select “no” and continue with question 50. If it is unknown if abnormalities were present or if no CT/CAT/MRIs were performed, select “unknown” and continue with question 50.

**Question 49: Date scan was performed:**

Enter the date the radiological assessment was performed.

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 50: Were there any clinical neurologic abnormalities present?**

Based on a clinical neurologic assessment, indicate if there were any clinical neurological abnormalities between diagnosis and the start of the preparative regimen. Neurologic abnormalities include abnormal gait, cranial nerve palsies, developmental delay, motor weakness, seizures, and sensory deficits. If clinical neurological abnormalities were present between diagnosis and the start of the preparative regimen, select “yes” and continue with question 51. If no clinical neurologic abnormalities were present, select “no” and continue with question 59. If it is not known if clinical abnormalities were present, select “unknown.”

**Questions 51-58: Specify neurologic abnormalities:**

Indicate the clinical neurological abnormalities present between diagnosis and prior to the start of the preparative regimen. Select “yes” or “no” for each question and ensure that no question is left blank. If a neurological abnormality is not listed but was present, select “yes” for question 57 (“other neurologic abnormality”) and specify the abnormality using question 58.

**History of Infection at Any Time Prior to the Preparative Regimen**

Specify documented infection(s) associated with HLH.

**Question 59: Was an infection documented?**

Indicate if an infection associated with HLH was present at any time prior to the start of the preparative regimen. If the recipient developed an infection associated with HLH prior to the start of the preparative regimen, select “yes” and continue with question 60. If there is no documentation of an infection associated with HLH, select “no” and continue with question 75.

**Question 60: Cytomegalovirus (CMV):**

Cytomegalovirus (CMV), also known as human herpesvirus 5 (HHV5), is one of the human herpes viruses (*Herpesviridae* family) and is very common, with an estimated 50-80% of individuals in the United States being infected by age 40. In healthy individuals, infection with CMV may not lead to any symptoms; however, the virus will lay dormant in the body after initial infection and can reoccur. In immunocompromised patients, such as immunosuppressed transplant recipients or HIV/AIDS patients, the virus can have serious consequences such as pneumonia, liver failure, and death.

If the recipient has a documented history of CMV associated with HLH, select “yes” and continue with question 61. If the recipient does not have a documented history of CMV, select “no” and continue with question 62.

**Question 61: Specify the test method used for diagnosis of CMV:**

Indicate the method used to diagnosis the CMV infection. The antigen method detects PP65 CMV proteins in leukocytes using an immunofluorescence assay. A PCR test is a molecular method to quantify the copies of CMV virus present in the sample. The shell

vial test is performed by inoculating a culture within a shell vial with the specimen, incubating the culture, and staining to detect CMV. Indicate if the method used to diagnose CMV infection was “antigen,” “PCR,” or “shell vial test.”

**Question 62: Epstein-Barr virus (EBV):**

Epstein-Barr Virus (EBV) is one of the human herpes viruses (*Herpesviridae* family). EBV infection may cause infectious mononucleosis, particularly in young adults. Infectious mononucleosis symptoms include fever, sore throat, lymphadenopathy, and fatigue. After initial infection, the virus will lay dormant in the body and can reoccur; recurrence of EBV is often subclinical. Late events associated with prior EBV infection include Burkitt’s Lymphoma and nasopharyngeal carcinoma.

If the recipient has a documented history of EBV associated with HLH, select “yes” and continue with question 63. If the recipient does not have a documented history of EBV, select “no” and continue with question 71.

**Question 63: In situ hybridization:**

*In situ* hybridization refers to the use of labeled viral probes to detect virus nucleic acids in tissue. Specify if the results of the in situ hybridization were “positive,” “negative,” or “not done” for EBV.

**Question 64: Polymerase chain reaction (PCR):**

Polymerase chain reaction (PCR) amplifies viral DNA to determine if the patient has a current primary infection or reactivated infection. Specify if the results of the PCR were “positive,” “negative,” or “not done” for EBV.

**Question 65: Serology:**

Serologic testing may be used to determine the presence of EBV antigen or antibodies to EBV. Specify if the results of the serology(s) were “positive,” “negative,” or “not done” for EBV. If “positive,” continue with question 66. If “negative” or “not done,” continue with question 70.

**Questions 66-69: Specify titers:**

Antibody titration to four EBV-specific markers can provide distinct information about whether a patient has a current primary or reactivated infection, recent infection, or past dormant infection. Antibodies to EBV nuclear antigen (**EBNA**) are not seen during acute infection, but develop 2-4 months after the first presentation of infection and persist for life. **Early antigen** testing measures IgG antibodies to early antigen; this generally appears at acute onset and is only detectable for 3-6 months. **Viral capsid IgG** measures IgG antibodies to viral capsid antigen that appear 2-4 weeks after presentation and persist for life. **Viral capsid IgM** testing for IgM antibodies to viral capsid antigen indicates current or recent infection, as it is generally only detectable for 4-6 weeks following first presentation.

Specify each EBV serologic antibody test as “positive” or “negative” in questions 66-69. Do not leave any response blank, unless testing failed, was inconclusive, or was not performed. If a validation error occurs due to the blank field, override the error.

**Question 70: Was documentation submitted to the CIBMTR?**

Indicate if a copy of the EBV results are attached. Use the Log of Appended Documents (Form 2800) to attach a copy of EBV result report(s). Attaching a copy of the report may prevent additional queries.

**Question 71: Other infection:**

Indicate if the recipient had an infection other than CMV or EBV associated with HLH at any time prior to the preparative regimen. If the recipient had an infection other than CMV or EBV, select “yes” and continue with question 72. If the recipient had no other documented infections associated with HLH, select “no” and continue with question 75.

**Questions 72-74: Organism and Site:**

For each infection, report the organism and site. Copy questions 72-74 for each infection.

**72. Other infection:**

Specify the other viral, bacterial, fungal, or parasitic infection.

**73. Organism:**

From the list “Codes for Commonly Reported Organisms,” select the code corresponding to the identified or suspected organism as reported on the microbiology report, laboratory report, or other physician documentation. Report the code in the boxes provided. If the specific organism is not listed, use the “other, specify” code (198 - bacteria, 209 - *Candida*, 219 - *Aspergillus*, 259 - fungus, 329 - virus, 409 - parasite) and report the name of the organism in the space provided. If the source of the infection is not determined, use code 509.

**74. Site:**

From the list “Codes for Common Sites of Infection,” select the code corresponding to the site of the infection.

If three or more sites are infected with the same organism, enter code 2 (Disseminated - generalized, isolated at 3 or more distinct sites).

**NOTE: Disseminated Infections**

The CIBMTR acknowledges that a discrepancy exists between the CIBMTR definition (3 or more sites) and the BMT-CTN definition (2 or more sites) for disseminated infections. For the purposes of this form, please use “disseminated” when the same organism is isolated at **three** or more distinct sites.

## Pre-HCT Therapy

Copy questions 76-107 to report more than one line of therapy.

### **Question 75: Was therapy given?**

Indicate if the recipient received therapy for HLH between diagnosis and the start of the preparative regimen. If the recipient received therapy, select “yes” and continue with question 76. If the recipient did not receive therapy, select “no” and continue with question 108.

### **Question 76: Specify the purpose of therapy:**

Induction therapies are the initial lines of therapy given to a recipient to bring them into remission. Maintenance therapies are designed to keep the recipients in remission; for some patients with HLH, maintenance is used as an ongoing treatment until a suitable donor can be found for an HCT. If HLH reactivates or relapses following induction therapy or during maintenance therapy, additional therapy is given to treat the reactivation/relapse. Indicate if the line of therapy being reported is “induction,” “maintenance,” or “treatment for disease relapse/reactivation.”

### **Questions 77-78: Date therapy started:**

Indicate if the therapy start date is “known” or “unknown.” If the therapy start date is known, use question 78 to enter the date the recipient began this line of therapy.

### **Questions 79-90: Specify therapy given:**

Systemic treatments vary based on protocol and in many cases are administered in the outpatient setting. A treatment may consist of a single drug or a combination of drugs. Additionally, the drugs may be administered on one day, over consecutive days, or continuously. Indicate “yes” or “no” for each therapy regimen or drug administered for the line of therapy being reported. Do not leave any responses blank. If the recipient received a therapy that is not listed, check “yes” for “other therapy” and specify the treatment in question 90. Report the generic name of the agent, not the brand name.

### **Question 91: Was this therapy given following the HLH-94/HLH 2004 protocol of the Histiocyte Society?**

Indicate if the therapy followed the HLH-94/HLH 2004 protocol of the Histiocyte Society. These protocols are meant to bring the recipient into remission, and then maintain their remission until an HCT can be performed. HLH-94 is a protocol that consists of 8 weeks of induction therapy with Etoposide and Dexamethasone followed by continuation therapy with etoposide, dexamethasone, and cyclosporine until transplant or reactivation of disease. Intrathecal methotrexate may be used in patients who have progressive neurological symptoms or CSF abnormalities. HLH 2004 is a protocol that adds cyclosporine to the induction therapy phase and proceeds similarly to HLH-94.\* For the purposes of this form, the induction and continuation phases of these protocols can be reported as one line of therapy. Prior to transplant, the patient receives a

preparative regimen that is separate from these protocols and should be reported on the Form 2000, but should not be included on this form as a line of therapy.

\*Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: Diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. *Pediatr Blood Cancer*. V 2007;48(2):124-31.

**Question 92: Was CNS disease inactive?**

Following this line of therapy, indicate if the recipient's CNS disease was inactive. Indicate "yes" or "no" and continue with question 93 to report specific response(s). If "unknown," continue with question 97.

**Question 93: Normal or stable CT or MRI of CNS:**

Based on CT or MRI of the central nervous system, indicate if previous CNS abnormalities have normalized or stabilized in response to this line of therapy. If the results of the CT or MRI are normal or stable, select "yes." If there was evidence of new, recurrent, or progressive CNS abnormality, indicate "no." If the response of CNS abnormalities assessed by CT or MRI is unknown, or if CT or MRI was not performed following the line of therapy, indicate "unknown."

**Question 94: Neopterin level:**

Indicate the neopterin level in the cerebrospinal fluid (CSF) following this line of therapy. Indicate "normal" or "elevated." If an assessment of neopterin levels in the CSF was not done following this line of therapy, select "not done."

**Question 95: Protein level:**

Indicate the protein level in the cerebrospinal fluid (CSF) following this line of therapy. Indicate "normal" or "elevated." If an assessment of protein levels in the CSF was not done following this line of therapy, select "not done."

**Question 96: WBC level:**

Indicate the WBC count in the cerebrospinal fluid (CSF) following this line of therapy. Indicate "normal" if there were less than or equal to 5 cells/ $\mu$ L in the CSF. Indicate "elevated" if there were greater than 5 cells/ $\mu$ L in the CSF. If an assessment of WBC count in the CSF was not done following this line of therapy, select "not done."

**Question 97: Was systemic disease inactive?**

Indicate if systemic disease consistent with the recipient's disease was inactive. Assessments of systemic disease include neutrophil count, hemoglobin level, hepatomegaly and splenomegaly evaluation, fibrinogen levels, triglyceride levels, and platelet counts. If the recipient's systemic disease was inactive following this line of therapy, indicate "yes" and continue with question 98. If the recipient's systemic disease was not inactive following this line of therapy, continue with 98. If the status of the recipient's systemic disease was unknown following this line of therapy, select "unknown" and continue with question 105.

**Question 98: ANC > 1.0 x 10<sup>9</sup>/L (without growth factor support):**

Indicate if the recipient's absolute neutrophil count (ANC) was greater than 1.0 x10<sup>9</sup>/L following this line of therapy, without the use of growth factors (e.g., filgrastim). Indicate "yes," "no," or "unknown."

**Question 99: Hemoglobin ≥ 9 g/dL without transfusion:**

Indicate if the recipient's hemoglobin level was equal to or greater than 9 g/dL without the use of red blood cell transfusions (within 30 days before test) following this line of therapy. Indicate "yes," "no," or "unknown."

**Question 100: Hepatomegaly resolved (≤ 3 cm below costal margin):**

Indicate if hepatomegaly was no longer present on physical examination following this line of therapy. Indicate "yes," "no," or "unknown."

**Question 101: Normal fibrinogen:**

Indicate if the fibrinogen level (factor I; fibrinogen activity; functional fibrinogen; fibrinogen antigen) returned to normal following this line of therapy. Indicate "yes," "no," or "unknown."

**Question 102: Normal triglycerides:**

Indicate if the triglyceride level has returned to normal following this line of therapy. Indicate "yes," "no," or "unknown."

**Question 103: Platelets > 100 x 10<sup>9</sup>/L without transfusion:**

Indicate if the recipient's platelet count was greater than 100 x10<sup>9</sup>/L without the use of platelet transfusions (within 7 days before test) following this line of therapy. Indicate "yes," "no," or "unknown."

**Question 104: Splenomegaly resolved (≤ 3 cm below costal margin):**

Indicate if splenomegaly was no longer present on physical examination following this line of therapy. Indicate "yes," "no," or "unknown."

**Question 105: Were there any signs of disease relapse/reactivation?**

Indicate if there were any signs of relapsed or reactivated disease following this line of therapy. 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 following this line of therapy, select "yes" and continue with question 106. If there was no evidence of disease relapse or reactivation following this line of therapy, select "no" and continue with question 108.

**Question 106: Specify the date of the relapse / reactivation:**

Indicate the date that relapse or reactivation was detected. Use the date of the radiological exam where relapse/reactive was determined, the date of the clinical neurologic exam, or the date the sample was collected for systemic disease 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 107: Specify the site of the relapse/reactivation:**

Indicate if the site of relapse was CNS, systemic, or CNS and 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 hepatosplenomegaly evaluations.

**Clinical Features and Laboratory Studies At Last Evaluation Prior to the Start of the Preparative Regimen**

**Question 108: Anemia (Hgb < 9 g/dL):**

Indicate if the recipient had anemia at the last evaluation prior to the start of the preparative regimen. Anemia is defined as hemoglobin less than 9 g/dL. Select “yes,” “no,” or “unknown.”

**Question 109: Degranulation assay of NK cells (as defined by local laboratory):**

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 results of degranulation assay of NK cells were “normal,” “abnormal,” or “unknown” at the last evaluation prior to the start of the preparative regimen.

**Question 110: Fever (> 38.5° C or > 101.3° F for > 7 days):**

Indicate if the recipient had fever at the last evaluation prior to the start of the preparative regimen. Fever is defined as a temperature above 38.5° C (101.3° F) for more than 7 days. Select “yes,” “no,” or “unknown.”

**Question 111: Hepatomegaly (liver edge palpable > 3 cm below right costal margin):**

Indicate if the recipient had hepatomegaly (enlargement of the liver) at the last evaluation prior to the start of the preparative regimen. 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 112-113: Serum ferritin:**

Indicate if the serum ferritin level was known at the last evaluation prior to the start of the preparative regimen. If “known,” indicate the value in question 113. If “unknown,” continue with question 114.

**Questions 114-115: Triglycerides:**

Indicate if the triglyceride level was known at the last evaluation prior to the start of the preparative regimen. If “known,” indicate the value in question 115. If “unknown,” continue with question 116.

**Questions 116-117: Fibrinogen antigen assay (factor I; fibrinogen activity; functional fibrinogen; fibrinogen antigen):**

Fibrinogen levels may be low in those with HLH. Indicate if a fibrinogen antigen assay (factor 1; fibrinogen activity; functional fibrinogen; fibrinogen antigen) level was known at the last evaluation prior to the start of the preparative regimen. If “known,” indicate the value (and corresponding unit) in question 117. If “unknown,” continue with question 118.

**Question 118: NK cell function:**

NK cell function is measured by a cytotoxicity assay.

NK cell function (cytotoxicity) may be absent or reduced in those with HLH. Indicate the NK cell function at the last evaluation prior to the start of the preparative regimen. Select “absent ( $\leq 10\%$  lower limit of normal),” “decreased (11-50% lower limit of normal),” “normal,” or “unknown.”

**Question 119: Neutropenia ( $ANC < 1.0 \times 10^9/L$ ):**

Indicate if the recipient was neutropenic at the last evaluation prior to the start of the preparative regimen. Neutropenia is defined as an absolute neutrophil count (ANC) less than  $1.0 \times 10^9/L$ . Indicate “yes,” “no,” or “unknown.”

**Question 120: Soluble interleukin-2 receptor alpha chain (sCD25) (as defined by local laboratory):**

The presence of soluble interleukin-2 receptors (soluble IL-2R, sCD25) in the plasma indicates the activation of T cells. Elevated soluble IL-2R is indicative of prolonged T-cell activation, indicating a protracted immune response. Levels of soluble IL-2R differ based on age, so using age-based reference ranges is helpful to identify abnormal results\* Indicate the soluble IL-2R alpha chain level at diagnosis or prior to the start of therapy for HLH. 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.”

\*Zhang K, Filipovich AH, Johnson J, et al. Hemophagocytic Lymphohistiocytosis, Familial. 2006 Mar 22 [Updated 2013 Jan 17]. In: Pagon RA, Adam MP, Bird TD, et al., editors. GeneReviews™ [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2013. Accessed at: <http://www.ncbi.nlm.nih.gov/books/NBK1444/> on October 3, 2013.

**Question 121: Splenomegaly (spleen palpable > 3 cm below left costal margin):**

Indicate if the recipient had splenomegaly (enlargement of the spleen) at the last evaluation prior to the start of the preparative regimen. 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 122: Thrombocytopenia (platelets < 100 x 10<sup>9</sup>/L):**

Indicate if the recipient was thrombocytopenic at the last evaluation prior to the start of the preparative regimen. Thrombocytopenia is defined as a platelet count less than 100 x 10<sup>9</sup>/L. Indicate “yes,” “no,” or “unknown.”

**Question 123: Neopterin level:**

The measurement of neopterin in the CSF is useful to determine immune system activity. Indicate the neopterin level in the cerebrospinal fluid (CSF) at the last evaluation prior to the start of the preparative regimen. Indicate “normal” or “elevated.” If an assessment of neopterin levels in the CSF was not done at the last evaluation prior to the start of the preparative regimen, select “not done.”

**Question 124: Protein:**

Indicate the protein level in the cerebrospinal fluid (CSF) at the last evaluation prior to the start of the preparative regimen. Indicate “normal” or “elevated.” If an assessment of protein levels in the CSF was not done at the last evaluation prior to the start of the preparative regimen, select “not done.”

**Question 125: WBC count:**

Indicate the WBC count in the cerebrospinal fluid (CSF) at the last evaluation prior to the start of the preparative regimen. 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 at the last evaluation prior to the start of the preparative regimen, select “not done.”

**Question 126: Were central nervous system (CNS) abnormalities found on computed tomography (CT or CAT) or magnetic resonance imaging (MRI) scans?**

Indicate if radiology (CT, CAT, and/or MRI) detected any abnormalities in the central nervous system (brain and spinal cord) at the time of assessment prior to the preparative regimen. CNS abnormalities may include lesions, leptomeningeal enhancements, or edema.

If CNS abnormalities were detected on radiological examination, select “yes” and continue with question 127. If no CNS abnormalities were detected on radiological examination, select “no” and continue with the signature lines. If it is unknown if abnormalities were present or if no CT/CAT/MRIs were performed, select “unknown” and continue with the signature lines.

**Question 127: Specify date scan was performed:**

Enter the date the radiological assessment was performed.

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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](#).

**Signature Lines:**

The FormsNet3<sup>SM</sup> 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.