

CIBMTR[®]

CENTER FOR INTERNATIONAL BLOOD
& MARROW TRANSPLANT RESEARCH

Instructions for Multiple Myeloma / Plasma Cell Leukemia Pre-HSCT Data (Form 2016)

This section of the CIBMTR Forms Instruction Manual is intended to be a resource for completing the Multiple Myeloma / Plasma Cell Leukemia Pre-HSCT Data 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 liaison.

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Multiple Myeloma / Plasma Cell Leukemia Pre-HSCT Data

NOTE:

Many references are included from the “Clinical Research Professionals Data Management – Multiple Myeloma” presentation from February 23, 2010, at the BMT Tandem Meetings. This presentation is available at:

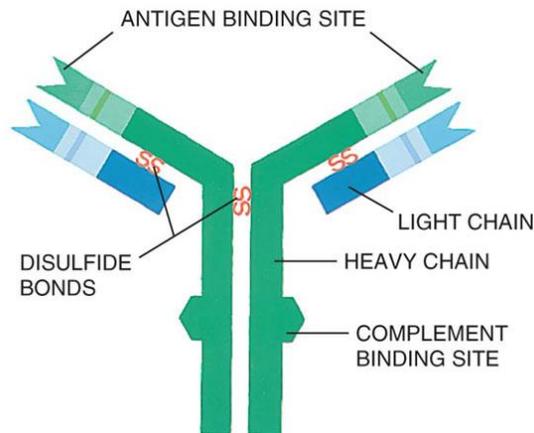
<http://www.cibmtr.org/Meetings/Materials/CRPDMC/Pages/fen10Hari.aspx>

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

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

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

Graphic 1: Structure of an Antibody



Secretory Multiple Myeloma:

Healthy plasma cells make immunoglobulins of all types. With the proliferation of malignant plasma cells, the level of one immunoglobulin type increases in the blood and/or urine. This abnormal immunoglobulin type is called the monoclonal immunoglobulin, monoclonal protein (M-protein/M-spike/M-component), or paraprotein. In most cases, the normal immunoglobulins are reciprocally depressed. Patients with this condition are said to have *secretory myeloma*.

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

Table 1. Distribution of Monoclonal Proteins in Secretory Multiple Myeloma

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

Nonsecretory Multiple Myeloma:

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

Table 2. Epidemiology of Multiple Myeloma in the United States

Cases diagnosed per year	~21,700
US Prevalence (2009)	~ 71,213
Median Age at Diagnosis	69 yrs
Sex	Higher incidence in men
Race	Higher incidence in African Americans
5-year survival rate	40%

"SEER Stat Fact Sheets: Myeloma." *Surveillance Epidemiology and End Results*. Web. 19 September 2012. <http://seer.cancer.gov/statfacts/html/mulmy.html>.

The Multiple Myeloma/Plasma Cell Leukemia Pre-HSCT Data Form is one of the Comprehensive Report Forms. This form captures multiple myeloma/PCL-specific pre-HSCT data such as: 1) the recipient's hematologic and laboratory findings at time of diagnosis and prior to start of preparative regimen, 2) pre-HSCT treatments administered, and 3) disease status prior to the preparative regimen.

This form must be completed for all recipients whose primary disease reported on Form 2000, question 9, is multiple myeloma, plasma cell leukemia (PCL), solitary plasmacytoma (no evidence of myeloma), or other plasma cell disorder (PCD).

Key Fields

Accuracy of the Key Fields is essential for ensuring that:

- Data are being reported for the correct recipient.
- Transplant centers have access to their data.
- Data are being shared with the correct donor center, cord blood bank, cooperative registry, or other approved agency.

For instructions regarding the completion of the Key Fields, see [Appendix K](#). Key fields include all fields listed in the *Center Identification* and *Recipient Identification* boxes.

NOTE:

If this is a report of a second or subsequent transplant, check the box and continue with question 132. The data that only occur once during the initial diagnosis should have already been reported.

Disease Assessment at Diagnosis

For each plasma cell disorder listed, indicate “yes” or “no.” Recipients may have more than one diagnosis. For example, the recipient may have been diagnosed with monoclonal gammopathy of unknown significance (MGUS) that progressed to multiple myeloma two years later.

If the diagnosis was determined at an outside center, and no documentation of a laboratory or pathological assessment is available, a dictated date within a physician note may be reported. Do not report the date symptoms first appeared. The date of diagnosis is important because the interval between diagnosis and HSCT is often a significant indicator for the recipient’s prognosis post-HSCT.

For multiple myeloma and PCL, if the exact pathological diagnosis date is not known, use the process described for reporting partial or unknown dates in General Instructions, [Guidelines for Completing Forms](#).

For the diagnoses that may have occurred earlier in the disease course and not well documented (solitary plasmacytoma, MGUS, amyloidosis), a “Date unknown” option is given on the form.

Question 1: Multiple myeloma

Diagnostic criteria for symptomatic multiple myeloma requires all three of the following:

- Monoclonal plasma cells in marrow ($\geq 10\%$) or biopsy-proven plasmacytoma

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

Question 2: Specify date of diagnosis of multiple myeloma

Report the date the recipient was first diagnosed with multiple myeloma. Enter the date the blood/urine was collected for the laboratory evaluations (e.g., serum/urine protein electrophoresis [SPEP/UPEP, respectively], serum/urine immunofixation) or enter the date of the first pathological diagnosis (e.g., bone marrow biopsy, plasmacytoma). Enter the date the sample was collected for examination.

Question 3: Plasma cell leukemia (PCL)

Plasma cell leukemia is a rare and aggressive plasma cell disorder. In PCL, the number of clonal plasma cells in the peripheral blood is $> 2 \times 10^9/L$ (> 2000 cells/mm³) or is $\geq 20\%$ of the leukocyte differential count. In addition, the neoplastic plasma cells may be found in extramedullary tissues, such as the spleen, liver, pleural effusions, ascites, and/or cerebrospinal fluid. PCL may be present de novo at the time of diagnosis (primary PCL) or evolve as a late feature in the course of multiple myeloma (secondary PCL).

Question 4: Specify date of diagnosis of PCL

Report the date the recipient was first diagnosed with PCL. Enter the date the blood was collected for the laboratory evaluations or enter the date of the first pathological diagnosis (e.g., bone marrow) of PCL. Enter the date the sample was collected for examination.

Question 5: Solitary plasmacytoma (in absence of bone marrow findings diagnostic for multiple myeloma or PCL)

A solitary plasmacytoma of bone (osseous plasmacytoma) is a localized bone tumor consisting of monoclonal plasma cells. Complete skeletal radiographs show no other lesions. There are no clinical features of plasma cell myeloma and no evidence of bone marrow plasmacytosis except for the solitary lesion. Localized plasma cell neoplasms that arise in tissues other than bone are called extraosseous (or extramedullary) plasmacytomas.

Question 6: Specify date of diagnosis of solitary plasmacytoma

Report the date of the first pathological diagnosis (e.g., biopsy) of plasmacytoma. Enter the date the sample was collected for examination.

Question 7: Monoclonal gammopathy of unknown significance (MGUS) prior to diagnosis for multiple myeloma or PCL

MGUS is defined as:

- The presence of a serum M-protein < 30g/L (< 3g/dl) without suppression of uninvolved immunoglobulins,
- Bone marrow clonal plasma cells < 10%,
- No end organ damage (CRAB), and
- No evidence of B-cell lymphoma (multiple myeloma, Waldenstrom's macroglobulinemia, amyloidosis) or other lymphoproliferative disorder known to produce an M-protein.

Question 8: Specify date of diagnosis of MGUS

Report the date the recipient was first diagnosed with MGUS. Enter the date the blood/urine was collected for the laboratory evaluations (e.g., serum/urine protein electrophoresis [SPEP/UPEP, respectively], serum/urine immunofixation) or report the date the bone marrow was collected for pathological evaluation.

NOTE: Question 9

This question relates to recipients who have amyloidosis with multiple myeloma (usually characterized as AA amyloidosis). If the recipient has primary amyloidosis alone (usually characterized as AL amyloidosis), it should be reported on Form 2017 (Amyloidosis) and not on Form 2016 (Multiple Myeloma/Plasma Cell Leukemia).

Question 9: Amyloidosis (at any time)

Systemic amyloidosis has been classified into three major types: primary (AL), secondary (AA), or hereditary (ATTR). These are distinguished by a two-letter code that begins with "A" for amyloid. The second letter of the code stands for the protein that accumulates in the tissues in that particular type of amyloidosis.

Primary amyloidosis (AL) is usually caused by a plasma cell, or rarely a lymphoplasmacytic neoplasm, that secretes whole or fragments of abnormal immunoglobulin **light chains** that deposit in various tissues and organs including subcutaneous fat, kidney, heart, liver, gastrointestinal tissue, peripheral nerves, and bone marrow.

Secondary amyloidosis (AA amyloid) occurs as a result of an illness such as multiple myeloma, chronic infections, or chronic inflammatory diseases. This form of amyloidosis is associated with serum amyloid A protein (SAA), an acute phase protein.

Hereditary amyloidosis (ATTR) is a rare form of amyloidosis. The amyloid deposits are composed of the protein transthyretin, or TTRrare.

Question 10: Specify date of diagnosis of amyloidosis

Report the date of the first pathological diagnosis (e.g., biopsy) of amyloidosis. Enter the date the sample was collected for examination.

Laboratory Studies at Diagnosis

For questions 11-50, report values obtained at diagnosis or prior to the first treatment for multiple myeloma/PCL. If testing is performed multiple times prior to the start of the first treatment, report the last test before the start of treatment. If the recipient has multiple myeloma, **do not answer questions 11 and 12**, as they apply only to the diagnosis of PCL.

The recipient may have initially been diagnosed with multiple myeloma, but progressed to PCL prior to HSCT. In that circumstance, report diagnostic information from the diagnosis of PCL in questions 11-50.

Question 11: (For PCL only) Plasma cells in blood

Indicate if the percentage of plasma cells in the blood is “known” or “not known” at the time of PCL diagnosis. If “known,” report the percentage as documented on the laboratory report. If “not known” continue with question 12.

Question 12: (For PCL only) Absolute number of plasma cells in blood

Indicate if the absolute number of plasma cells in the blood is “known” or “not known” at the time of PCL diagnosis. If “known,” report the absolute number of plasma cells in the blood as determined by multiplying the total number of white blood cells (WBCs) by the percentage of plasma cells. Indicate the appropriate unit of measure. If “not known,” continue with question 13.

Question 13: Immunochemical type

Indicate whether the multiple myeloma is secretory or non-secretory. Non-secretory means that an M-protein is absent on serum or urine immunofixation. About 3% of plasma cell myelomas are referred to as non-secretory myeloma.

If “secretory,” continue with question 14. If “non-secretory,” continue with question 22.

NOTE: Questions 14-21

Specify the paraproteins present at diagnosis. This data reflects the serum and/or urine immunofixation results. Immunofixation detects the specific immunoglobulins (e.g., IgG kappa) after separating the proteins into bands on an electrophoresis gel.

Table 3. Concept of Clonality in Multiple Myeloma

Type of Myeloma	M-proteins Expressed
Plasma Cell Myeloma	One heavy chain (IgG, IgA, etc.) and one light chain (either kappa or lambda)
Biclonal Myeloma	Two different M-proteins (e.g., IgG Kappa and IgA Lambda)

NOTE:

For patients with light chain only disease, questions 14-17 will be left unanswered, resulting in a generated error for each question. Each error will require an override. Currently, FormsNet2™ does not allow these questions to be skipped for light chain only disease.

Questions 14 & 16: Heavy chain

Indicate the heavy chain type the multiple myeloma is secreting. IgG, followed by IgA are most commonly involved. IgD and IgE occur, but rarely. If more than one immunoglobulin is involved, provide documentation via the Log of Appended Documents (Form 2800). If IgM is involved, provide documentation that the disease is not Waldenstrom’s Macroglobulinemia, or switch to the MAC Form (2019) and update the Form 2400 & Form 2000 if MAC is the correct diagnosis.

Questions 15 & 17: Source (heavy chain)

Indicate whether the sample source was serum or urine.

Questions 18 & 20: Light Chain

Indicate the light chain type secreted by the multiple myeloma. If both light chains are involved, provide documentation via the Log of Appended Documents (Form 2800).

Questions 19 & 21: Source (light chain)

Indicate whether the sample source was serum or urine.

Question 22: WBC

Indicate if the WBC is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 23.

Question 23: Hemoglobin

Low hemoglobin values may indicate the presence of anemia if the values represent an untransfused state. Indicate whether the hemoglobin is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known” continue with question 25.

NOTE: Transfusions

Currently there is an error on the Form 2016 regarding transfusion history. The form should read: "Was RBC transfused in the prior \leq 30 days?"

Question 24: Was RBC transfused in the prior 30 days?

Indicate "yes" if red blood cells were transfused less than or equal to 30 days prior to obtaining the hemoglobin value reported in question 23; otherwise indicate "no."

Question 25: Platelets

Indicate whether the platelet count is "known" or "not known" at the time of multiple myeloma or PCL diagnosis. If "known," report the value and unit of measure documented on the laboratory report. If "not known" continue with question 27.

NOTE: Transfusions

Currently there is an error on the Form 2016 regarding transfusion history. The form should read: "Were platelets transfused in the prior \leq 7 days?"

Question 26: Were platelets transfused in the prior 7 days?

Indicate "yes" if platelets were transfused less than or equal to 7 days prior to obtaining the platelet value reported in question 25; otherwise indicate "no."

NOTE:

- Under normal circumstances, the marrow aspirate is used to obtain the differential cell count, review morphology of the cells, and perform cytogenetic studies, flow cytometry, etc. The biopsy is obtained to evaluate the overall cellularity of the marrow. In the case of myeloma, the marrow plasma cells tend to be a patchy infiltrate rather than a diffuse infiltrate as in the case of acute leukemia. Therefore, it is possible that the plasma cell numbers may vary between the aspirate and biopsy.
- The percentage of plasma cells in the bone marrow aspirate and/or biopsy may also be identified on a flow cytometry report. A flow cytometry report may NOT be used as source documentation when reporting the data for questions 27-29.
- If the bone marrow pathology report states a range for plasma cells, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
- If the report states > 90% plasma cells, enter 91% on the form.
- If the report states a marrow packed with plasma cells or sheets of plasma cells, report 99% on the form.
- If the report states < 5% plasma cells, enter 4% on the form.

Question 27: Plasma cells in bone marrow aspirate

Indicate whether the plasma cells in the bone marrow **aspirate** are "known" or "unknown" at the time of multiple myeloma or PCL diagnosis. If "known," report the percentage of plasma cells in the bone marrow aspirate documented on the pathology

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report. Question 29 should then be answered “not known.” If “not known,” continue with question 28.

Question 28: Plasma cells in bone marrow biopsy

Indicate whether the plasma cells in the bone marrow **biopsy** are “known” or “unknown” at the time of multiple myeloma or PCL diagnosis. If “known,” report the percentage of plasma cells in the bone marrow biopsy documented on the pathology report. Question 29 should then be answered “not known.” If “not known,” continue with question 29.

Question 29: Plasma cells in bone marrow, sample source unknown

Question 29 is to be answered when it is unclear from the source documentation whether the sample source was the marrow aspirate or the marrow biopsy. If that is the case, then indicate “known” and report the percentage of plasma cells as documented; and verify that questions 27-28 are answered “not known.” If “not known,” continue with question 30.

Question 30: Serum albumin

Indicate whether the serum albumin is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 31.

Question 31: Serum β 2 microglobulin

At the time of multiple myeloma or PCL diagnosis, an elevated serum β 2 microglobulin protein may indicate a poorer prognosis. If this value is “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 32.

Table 4. International Staging System (ISS)

Stage	Criteria
Stage I	β 2 microglobulin < 3.5 mg/dL, albumin \geq 3.5 g/dL
Stage II	β 2 microglobulin 3.5 g/dL – 5.4 g/dL or albumin < 3.5 g/dL
Stage III	β 2 microglobulin \geq 5.5 g/dL

NOTE: Question 32

If questions 30 & 31 are “known,” then question 32 should not be answered. If questions 30 & 31 are “unknown,” question 32 must be answered, but can also be answered as “unknown.”

The ISS stage is not the same as the Durie-Salmon stage, which uses different criteria (the amount of monoclonal protein, hemoglobin, etc.) to determine the myeloma stage.

Question 32: If questions 30 and 31 are “not known,” what was the International Staging System (ISS) stage at diagnosis?

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The CIBMTR calculates the ISS stage based on the values reported in questions 30 and 31. If the laboratory values for question 30 and/or question 31 are “not known,” and the center knows the ISS stage, it should be reported here. If the ISS stage at diagnosis is unknown and the laboratory values in questions 30 & 31 are unknown, indicate “unknown,” and continue with question 33.

Question 33: Serum calcium

Indicate whether the serum calcium is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 34.

NOTE: Serum Creatinine

Currently there is an error on Form 2016, question 34. “Non-secretory” should not be an option and should be disregarded when completing this data field.

Question 34: Serum creatinine

Indicate whether the serum creatinine is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the laboratory value and unit of measure documented on the laboratory report and continue with question 35. If “not known,” continue with question 36.

Question 35: Upper limit of normal for serum creatinine

Indicate the upper limit of normal for serum creatinine value used at your institution.

NOTE: Serum Monoclonal Ig

Question 36 is intended to capture the M-protein value identified on the serum electrophoresis (SPEP) at diagnosis. Do not report immunofixation results here.

Question 36: Serum monoclonal Ig: (only from electrophoresis) (monoclonal (M-spike) protein level) (This value will be used to calculate the best response to HSCT if question 131 is answered as option 1.)

Monoclonal gammopathy is defined as the increased production of one type of Ig by a single clone of cells. The abnormal protein produced is called paraprotein or M-protein. Indicate whether the serum monoclonal Ig is “known” or “not known” at the time of the multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known” or “non-secretory,” continue with question 37.

For recipients with biclonal myeloma, report the serum monoclonal Ig with the largest quantity.

NOTE: Urinary Monoclonal Light Chains

Question 37 is intended to capture the 24-hour urine light chain results, not the 24-hour protein excretion. The results will be reported as XX g in 24-hours of kappa or lambda light chains, or XX g/dL. If the value is reported in XX g/dL, it can be multiplied by the volume of the urine to determine the 24-hour urine light chains.

For example: (total in g/dL of the light chain) x (total urine volume) = urinary monoclonal light chains/24 hours (0.145 g/dL of lambda light chains) x (1500 mL total urine) = 2.175 g/24 hours.

Do not report immunofixation results here.

Question 37: Urinary monoclonal light chains

Indicate whether the amount of urinary monoclonal light chains is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. The value reported here should be based on a 24 hour urine collection. If “known,” report the laboratory value. If “not known,” continue with question 38.

Question 38: Serum free light chains – κ (kappa)

Indicate whether the serum κ (kappa) free light chain level is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 40.

Question 39: Upper limit of normal for κ free light chain

Indicate the upper limit of normal for κ (kappa) free light chains value and unit of measure used at your institution.

Question 40: Serum free light chains – λ (lambda)

Indicate whether the serum λ (lambda) free light chain level is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 42.

Question 41: Upper limit of normal for λ free light chain

Indicate the upper limit of normal for λ (lambda) free light chains value and unit of measure used at your institution.

Question 42: LDH

Indicate whether the LDH (lactate dehydrogenase) level is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 44.

Question 43: Upper limit of normal for LDH

Indicate the upper limit of normal for LDH value and unit of measure used at your institution.

Question 44: IgG

Indicate whether the IgG level is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 47.

Question 45: Upper limit of normal for IgG

Indicate the upper limit of normal for IgG value used at your institution.

Question 46: Lower limit of normal for IgG

Indicate the lower limit of normal for IgG value used at your institution.

Question 47: IgA

Indicate whether the IgA level is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 50.

Question 48: Upper limit of normal for IgA

Indicate the upper limit of normal for IgA value used at your institution.

Question 49: Lower limit of normal for IgA

Indicate the lower limit of normal for IgA value used at your institution.

Question 50: IgM

Indicate whether the IgM level is “known” or “not known” at the time of multiple myeloma or PCL diagnosis. If “known,” report the value and unit of measure documented on the laboratory report. If “not known,” continue with question 53.

Question 51: Upper limit of normal for IgM

Indicate the upper limit of normal for IgM value used at your institution.

Question 52: Lower limit of normal for IgM

Indicate the lower limit of normal for IgM value used at your institution.

Pre-HSCT Treatment For Plasma Cell Disorders

NOTE: Paper forms submission

When submitting the paper version of the form for more than two lines of therapy, copy the “Pre-HSCT Treatment for Plasma Cell Disorders” section for each line of therapy administered. Check the box to indicate additional pages are attached. The FormsNet2™ application allows for multiple lines of therapy to be reported. Complete a “Line of Therapy” section for each line of therapy administered prior to the start of the preparative regimen.

A line of therapy is one or more cycles of a defined treatment program given to a patient with no progression of disease in between. A new line of therapy starts when a new agent(s) is added or changed due to relapse, progression, and/or toxicity; or after a period of observation when a new agent is started for progression or relapse.

Example A: A 62 year old man is diagnosed with IgG Kappa multiple myeloma. He receives initial therapy with 6 cycles of bortezomib and lenalidomide/dexamethasone; and achieves a very good partial response (VGPR). None of the treatment drugs were changed and there was no disease progression. He then receives an autologous transplant. One line of therapy should be reported for this patient in questions 54-91.

Example B: A 69 year old woman is diagnosed with IgA Lambda multiple myeloma. She receives bortezomib and thalidomide/dexamethasone as initial treatment. A few months after the start of therapy, her test results indicate progressive disease. She is then treated with lenalidomide/dexamethasone and achieves a partial response (PR). The patient receives high-dose cyclophosphamide as part of an autologous stem cell harvest. Three lines of therapy should be reported for this patient.

Question 53: Was therapy given between diagnosis and the start of the preparative regimen?

Indicate if the recipient received treatment for a plasma cell disorder (e.g., multiple myeloma and/or PCL) between the time of diagnosis and the preparative regimen. If “yes,” continue with question 54. If “no,” continue with question 130.

Question 54 or 92: Systemic Therapy

Systemic therapy (e.g., chemotherapy) may be injected into a vein or given orally and is delivered to the whole body via the bloodstream. If “yes,” continue with question 55 or 93. If “no,” continue with question 78 or 116.

Question 55 or 93: Date therapy started

Enter the date the recipient began this line of therapy.

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

Question 56 or 94: Date therapy stopped

If the recipient received therapy administered in cycles, report the date the recipient started the last cycle for this line of therapy.

If the recipient received therapy administered on a daily basis (e.g. lenalidomide therapy at 10 mg/day) report the last date the recipient received the line of therapy.

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

Question 57 or 95: Number of cycles

Systemic therapy (e.g., chemotherapy, monoclonal Abs) is usually administered in cycles with rest periods between the cycles. This enables cancer cells to be attacked at vulnerable times and provides healthy cells adequate time to recover from the damage. A cycle can last one or more days and may repeat weekly, bi-weekly, or monthly. A systemic therapy course may consist of multiple cycles. Enter the number of cycles the recipient received during the line of therapy being reported, or check “unknown/not applicable.”

Questions 58-77 or 96-115: Treatment

Systemic treatments vary based on protocol and in most 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 chemotherapy treatment drug administered for the line of therapy being reported. Do not leave any responses blank. If the recipient received a chemotherapy treatment that is not listed, check “yes” for “other systemic therapy” and specify the treatment in question 77 or 115. Report the generic name of the agent, not the brand name.

Question 78 or 116: Supportive Care

Supportive care includes bisphosphonate therapy, erythroid stimulants, kyphoplasty, and/or vertebroplasty. Bisphosphonate therapy is a class of drugs used to slow down or prevent bone loss, e.g., Aredia and Zometa. Erythroid stimulants are used to treat anemia by stimulating the bone marrow to produce more red cells, e.g., Procrit and Aranesp. Kyphoplasty is a surgical procedure used to treat painful, progressive vertebral compression fractures. Kyphoplasty is performed by inserting a special balloon into the cavity created in the fractured bone. The space created by the balloon is filled with PMMA, a type of acrylic cement. Vertebroplasty is also a surgical procedure used to treat painful vertebral fractures. Vertebroplasty does not use a balloon to create a space, but utilizes 1-2 needles inserted in the fractured vertebrae through which acrylic bone cement is pushed. Indicate “yes” if the recipient was treated with supportive care. If “no,” continue with question 84 or 122.

Questions 79-82 or 117-120: Treatment

Indicate “yes” or “no” for each supportive care treatment listed that the recipient may have received. Do not leave any responses blank.

Question 83 or 121: Specify number of vertebrae

If question 81 or 82 (119 or 120) is “yes,” indicate the number of vertebrae that were treated with kyphoplasty or vertebroplasty.

Question 84 or 122: Radiation Therapy

Radiation therapy utilizes high-energy radiation to kill cancer cells. For multiple myeloma, external beam radiation is the type of radiation is used most frequently. In this method, a beam of radiation is delivered to a specific part of the body, such as a lytic lesion or plasmacytoma. Indicate if the recipient received radiation therapy between the time of diagnosis and the start of the preparative regimen. If “yes,” continue with question 85 or 123. If “no,” continue with question 87 or 125.

Question 85 or 123: Date therapy started

Enter the date the line of radiation therapy began.

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

Question 86 or 124: Date therapy stopped

Enter the date the line of radiation therapy ended.

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

Question 87 or 125: Was this line of therapy given for stem cell priming?

Indicate “yes” if this line of therapy was given for stem cell priming. For example, high dose cyclophosphamide (Cytoxan) may be used in a myeloma patient to collect their peripheral blood stem cells (PBSCs) as they recover their white blood count. Answer “no” if this line of therapy was not given for stem cell priming.

Question 88 or 126: Best response to line of therapy

Indicate the best response to the line of therapy.

For more information on determining what baseline values to use to establish best response, see [Appendix V](#) and [Appendix W](#).

Table 5. Best Response to Line of Therapy Definitions

Best Response	Definition
<p>Stringent Complete Remission (sCR)</p>	<p>Follow criteria for CR as defined below, plus all of the following:</p> <ul style="list-style-type: none"> • Normal free light chain ratio, • Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence (confirmation with repeat bone marrow biopsy not needed). (Presence and/or absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting the presence of an abnormal clone is κ/λ of $> 4:1$ or $< 1:2$.) <p>sCR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy sCR requirements.</p>
<p>Complete Remission (CR)</p>	<p>A treatment response where all of the following criteria are met:</p> <ul style="list-style-type: none"> • Negative immunofixation on serum and urine samples • Disappearance of any soft tissue plasmacytomas • $< 5\%$ plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed) <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p style="text-align: center;">NOTE: CR Requirements</p> <p>For recipients with light chain only myeloma, all of the following criteria must be met:</p> <ul style="list-style-type: none"> • Normal serum free light chain ratio • Negative immunofixation on urine samples • Disappearance of any soft tissue plasmacytomas • $< 5\%$ plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed) <p>For recipients with non-secretory myeloma, all of the following criteria must be met:</p> <ul style="list-style-type: none"> • Disappearance of all soft tissue plasmacytomas • $< 5\%$ plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed) </div>

<p>Complete Remission (CR) (cont.)</p>	<p>CR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy CR requirements.</p>
<p>Very Good Partial Response (VGPR)</p>	<p>One or more of the following must be present:</p> <ul style="list-style-type: none"> • Serum and urine M-protein detectable by immunofixation but not on electrophoresis • $\geq 90\%$ reduction in serum M-protein and urine M-protein level < 100 mg/24 hours. <p>VGPR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy VGPR requirements.</p>
<p>Partial Response (PR)</p>	<p>Both of the following must be present:</p> <ul style="list-style-type: none"> • $\geq 50\%$ reduction in serum M-protein • Reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg/24 hours. <p>If the serum and urine M-protein are not measurable (i.e., do not meet the following criteria):</p> <ul style="list-style-type: none"> • serum M-protein ≥ 1 g/dL, • urine M-protein ≥ 200 mg/24 hours; <p>then a $\geq 50\%$ decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (provided the serum free light chain assay shows involved level > 10 mg/dL and the serum free light chain is abnormal).</p> <p>If serum and urine M-protein <i>and</i> serum-free light assay are not measurable, a $\geq 50\%$ reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline bone marrow plasma cell percentage was $\geq 30\%$.</p> <p>In addition to the above listed criteria, a $\geq 50\%$ reduction in the size of soft tissue plasmacytomas is also required, if present at baseline.</p> <p>PR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy PR requirements.</p>

<p>Stable Disease (SD)</p>	<p>Does not meet the criteria for CR, VGPR, PR, or PD. SD requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy SD requirements.</p>
<p>Progressive Disease (PD)</p>	<p>Requires one or more of the following: Increase of $\geq 25\%$ from the lowest response value achieved in:</p> <ul style="list-style-type: none"> • Serum M-component with an absolute increase ≥ 0.5 g/dL (for progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient if the starting M-component is ≥ 5 g/dL); and/or • Urine M-component with an absolute increase ≥ 200 mg/24 hours; and/or • For recipients without measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL; and/or • Bone marrow plasma cell percentage with absolute percentage $\geq 10\%$; and/or • Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas; and/or • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol) that can be attributed solely to the plasma cell proliferative disorder. <p>PD requires two consecutive assessments (of the same method) made at any time before classification as disease progression, and/or the institution of any new therapy.</p>
<p>Relapse from CR (untreated)</p>	<p>Requires one or more of the following:</p> <ul style="list-style-type: none"> • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; and/or • Development of $\geq 5\%$ plasma cells in the bone marrow (relapse from CR has a 5% cutoff vs. 10% for other categories); and/or • Appearance of any other sign of progression (e.g., new plasmacytoma, lytic bone lesion, hypercalcemia). <p>Relapse requires two consecutive assessments (of the same method) made at any time before classification as relapse, and/or the institution of any new therapy.</p>

At any response level, if some but not all criteria met, the best response should be downgraded to next lower level of response.

The percentage of plasma cells in the bone marrow aspirate and/or biopsy may also be identified on a flow cytometry report. A flow cytometry report may **NOT** be used to confirm CR (e.g., < 5% plasma cells in the bone marrow).

Question 89 or 127: Date response established

Enter the date the best response began. Report the date of the first assessment, not the date of the second confirmatory assessment. Report the date the blood/urine was collected for the laboratory evaluations (e.g., SPEP/UPEP, serum/urine immunofixation) or report the date the bone marrow was collected for pathologic exam.

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

Question 90 or 128: Did disease relapse/progress following this line of therapy?

Indicate “yes” if a relapse or progression occurred following the line of therapy being reported and continue with question 91 or 129. Indicate “no” if the recipient did not relapse or progress following this line of therapy and continue with question 92 or 130.

Table 6. Relapse/Progression Definition

Disease Status	Definition
Progression	<p>Requires one or more of the following:</p> <p>Increase of $\geq 25\%$ from the lowest response value achieved in:</p> <ul style="list-style-type: none"> • Serum M-component with an absolute increase ≥ 0.5 g/dL (for progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if the starting M-component is ≥ 5 g/dL); and/or • Urine M-component with an absolute increase ≥ 200 mg/24 hours; and/or • For recipients without measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL; and/or • Bone marrow plasma cell percentage with absolute percentage $\geq 10\%$; and/or • Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas; and/or

<p>Progression (cont.)</p>	<ul style="list-style-type: none"> • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol) that can be attributed solely to the plasma cell proliferative disorder. <p>PR requires two consecutive assessments (of the same method) made at any time before classification as disease progression, and/or the institution of any new therapy.</p>
<p>Relapse from CR</p>	<p>Requires one or more of the following:</p> <ul style="list-style-type: none"> • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; and/or • Development of ≥ 5% plasma cells in the bone marrow (relapse from CR has a 5% cutoff vs. 10% for other categories); and/or • Appearance of any other sign of progression (e.g., new plasmacytoma, lytic bone lesion, hypercalcemia) <p>Relapse requires two consecutive assessments (of the same method) made at any time before classification as relapse, and/or the institution of any new therapy.</p>

Question 91 or 129: Date of relapse/progression

Enter the date the relapse or progression was established following the line of therapy. Report the date the blood/urine was collected for the laboratory evaluations (e.g., SPEP/UPEP, serum/urine immunofixation) or report the date the bone marrow was collected for pathological evaluation. However, if there was not a second assessment obtained prior to the start of new therapy, report the date the new therapy started as the date of relapse/progression. Continue with question 92 or 130.

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

If more than two lines of therapy were administered between diagnosis and the start of the preparative regimen, continue reporting each line as described at the beginning of this section. Continue to question 130 when all lines of therapy have been reported.

Question 130: Specify the sensitivity of myeloma to chemotherapy prior to the preparative regimen

Indicate “sensitive” disease if there has been ≥ 50% reduction in Ig level (M-protein), or ≥ 90% reduction in urinary light chains in light chain only disease, or ≥ 50% reduction in plasma cells in bone marrow for nonsecretory myeloma. This includes disease status of:

- Stringent Complete Remission (sCR)
- Complete Remission (CR)

- Very Good Partial Remission (VGPR)
- Partial Remission (PR)

Indicate “resistant” disease if there has been $\leq 50\%$ reduction in Ig level (M-protein), or $\leq 90\%$ reduction in urinary light chains in light chain only disease, or $\leq 50\%$ reduction in plasma cells in bone marrow for non-secretory myeloma. This includes disease status of:

- Stable Disease (SD)
- Progressive Disease (PD)

If no chemotherapy was given or chemotherapy ended > 6 months prior to the preparative regimen, indicate “not applicable” and continue with question 131. If the sensitivity to chemotherapy prior to the preparative regimen is unknown, check “unknown” and continue with question 131.

Question 131: At what point in the disease course was the HSCT performed?

If the HSCT was performed “as part of initial therapy for a recipient with no disease progression at any time prior to HSCT,” choose option 1. If the HSCT was performed “later in the disease course **or** for a recipient with disease progression at any time prior to HSCT,” choose option 2.

Example A: A 62 year old man is diagnosed with IgG Kappa multiple myeloma. He receives initial therapy with 6 cycles of bortezomib and lenalidomide/dexamethasone; and achieves a VGPR. None of the treatment drugs were changed and there was no disease progression. He then receives an autologous transplant. **Option 1** should be chosen for this patient, as there was no disease progression prior to the HSCT.

Example B: A 69 year old woman is diagnosed with IgA Lambda multiple myeloma. She receives bortezomib and thalidomide/dexamethasone as initial treatment. A few months after the start of therapy, her test results indicate progressive disease. She is then treated with lenalidomide/dexamethasone, and achieves a PR. The patient receives high-dose cyclophosphamide as part of an autologous stem cell harvest. **Option 2** should be reported for this patient since there was previous disease progression prior to HSCT.

Laboratory Studies Prior to the Start of the Preparative Regimen

NOTE:

- Under normal circumstances, the marrow aspirate is used to obtain the differential cell count, review morphology of the cells, and to perform cytogenetic studies, flow cytometry, etc. The biopsy is obtained to evaluate the overall cellularity of the marrow. In the case of myeloma, the marrow plasma cells tend to be a patchy infiltrate rather than a diffuse infiltrate as in the case of acute leukemia. Therefore, it's possible that the plasma cell numbers may vary between the aspirate and biopsy.
- The percentage of plasma cells in the bone marrow aspirate and/or biopsy may also be identified on a flow cytometry report. A flow cytometry report may NOT be used as source documentation when reporting the data for questions 132-134.
- If the bone marrow pathology report states a range for plasma cells, enter the average of the range rounded to the nearest whole number (e.g., if 0-5%, enter 3%).
- If the report states > 90% plasma cells, enter 91% on the form.
- If the report states a marrow packed with plasma cells or sheets of plasma cells, report 99% on the form.
- If the report states < 5% plasma cells, enter 4% on the form.

Question 132: Plasma cells in bone marrow aspirate

Indicate whether the plasma cell percentage in the bone marrow **aspirate** is "known" or "not known" prior to the start of the preparative regimen. If "known," report the percentage documented on the pathology report and question 134 should be answered "not known." If "not known," continue with question 133.

Question 133: Plasma cells in bone marrow biopsy

Indicate whether the plasma cell percentage in the bone marrow **biopsy** is "known" or "not known" prior to the start of the preparative regimen. If "known," report the percentage documented on the pathology report and question 134 should be answered "not known." If "not known," continue with question 134.

Question 134: Plasma cells in bone marrow, sample source unknown

Question 134 is to be answered when it is unclear from the source documentation whether the sample source was the marrow aspirate or the marrow biopsy. If that is the case, then indicate "known" and report the percentage of plasma cells as documented; and verify questions 132-133 are answered "not known." If "not known," continue with question 135.

Question 135: Serum albumin

Indicate whether the serum albumin is “known” or “not known” prior to the start of the preparative regimen. If “known,” report the laboratory value and unit of measure documented on the laboratory report. If “not known,” continue with question 136.

Question 136: Serum β 2 microglobulin

Indicate whether the serum β 2 microglobulin is “known” or “not known” prior to the start of the preparative regimen. If “known,” report the laboratory value and unit of measure documented on the laboratory report. If “not known,” continue with question 137.

NOTE: Serum Monoclonal Ig

Question 137 is intended to capture the M-protein value identified on the serum electrophoresis (SPEP) prior to the start of the preparative regimen.

Currently there is an error on the 2016 Form, question 137. It reads “this value will be used to calculate the best response to HSCT” and “this value will be used to calculate the best response to HSCT if question 131 is answered as option 2.” The form should read:

- If option 1 was selected, the values obtained at diagnosis will be used to determine best response to HSCT.
- If option 2 was selected, the values obtained at time of most recent progression/relapse will be used to determine best response to HSCT (i.e., progression/relapse resets the baseline)
- If option 2 was selected, and the patient has not received any chemotherapy within 6 months of the HSCT or has untreated relapse/progression, this value will be used to determine best response to HSCT.

Do not report immunofixation results here.

Question 137: Serum monoclonal Ig: (only from electrophoresis)

Monoclonal gammopathy is defined as the increased production of one type of immunoglobulin by a single clone of cells. The abnormal protein produced is called a paraprotein or M-protein. Indicate whether the serum monoclonal Ig is “known” or “not known” prior to the start of the preparative regimen. If “known,” report the laboratory value and unit of measure documented on the laboratory report. If “not known,” continue with question 138.

For recipients with biclonal myeloma, report the serum monoclonal Ig with the largest quantity.

Question 138: (For PCL only) Are circulating plasma cells currently present?

Indicate “yes” if there are circulating plasma cells in the peripheral blood for recipients with PCL. If there are no circulating plasma cells present indicate “no” and continue with question 139.

Question 139: Were cytogenetics tested (conventional or FISH)?

Cytogenetic assessment involves testing blood or bone marrow for the presence of a known cytogenetic abnormality that reflects the recipient’s disease. FISH is categorized with cytogenetics because its sensitivity is similar to standard cytogenetics. Indicate “yes” if cytogenetic studies were obtained at the time of multiple myeloma or PCL diagnosis **and/or** up to the start of the preparative regimen and continue with question 140.

If cytogenetic studies were obtained but there were not adequate cells (metaphases) to determine the results, check “yes,” and specify “no evaluable metaphases” in questions 140 and/or 141.

If no cytogenetic studies were obtained or it is unknown if chromosome studies were performed, indicate “no” or “unknown” and continue with question 181.

NOTE:

Even though flow cytometry has a similar sensitivity to FISH assays, it would not be appropriate to report those results here. Flow cytometry does not identify chromosomal abnormalities; FISH assays do.

Cytogenetics at diagnosis: If cytogenetics were not performed at this time point, leave question 140 blank and override the error in FormsNet™. Questions 142-160 should be left blank also.

Cytogenetics after diagnosis to prior to preparative regimen: If cytogenetics were not performed at this time point, leave question 141 blank and override the error in FormsNet2™. Questions 161-179 should be left blank also.

Question 140: Results of test at diagnosis

Indicate “yes” if chromosomal abnormalities were identified at the time of diagnosis or prior to start of any treatment for multiple myeloma or PCL and complete questions 142-160.

If the patient had a history of multiple myeloma with a subsequent diagnosis of PCL, report the cytogenetics from the time of PCL diagnosis.

If “no evaluable metaphases,” “no abnormalities,” or if cytogenetics were not tested at this time point, leave questions 142-160 blank and continue with question 141.

Question 141: Results of tests after diagnosis and prior to the preparative regimen

Indicate if any chromosomal abnormalities were identified at any time after multiple myeloma or PCL diagnosis and prior to the start of the preparative regimen. If tests were only performed at diagnosis, do not re-report in question 141 (and questions 161-179).

If “yes abnormalities identified,” complete questions 161-179.

If “no evaluable metaphases,” “no abnormalities,” or if cytogenetics were not tested at this time point, leave questions 161-179 blank and continue with question 180.

Questions 142-160: Specify abnormalities identified at diagnosis

Indicate “yes” or “no” for each cytogenetic abnormality identified at the time of multiple myeloma or PCL diagnosis. If the cytogenetic abnormality is “other abnormality,” specify the abnormality identified. Do not leave any response blank.

For more information regarding cytogenetic terminology and nomenclature, see [Appendix R](#), Cytogenetic Abbreviations and Terminology.

Questions 161-179: Specify abnormalities identified between diagnosis and preparative regimen

Indicate “yes” or “no” for each cytogenetic abnormality identified at any time after multiple myeloma or PCL diagnosis and/or up until the start of the preparative regimen. If the cytogenetic abnormality is “other abnormality,” specify the abnormality identified. Do not leave any response blank.

For more information regarding cytogenetic terminology and nomenclature, see [Appendix R](#), Cytogenetic Abbreviations and Terminology.

Question 180: Is a copy of the cytogenetic or FISH report attached?

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

Disease Status at the Last Evaluation Prior to the Preparative Regimen

Question 181: What was the disease status prior to the preparative regimen?

Indicate the disease status of multiple myeloma or PCL at the last evaluation prior to the start of the preparative regimen.

Table 7. Disease Status Definitions

Disease Status	Definition
<p>Stringent Complete Remission (sCR)</p>	<p>Follow criteria for CR as defined below, plus all of the following:</p> <ul style="list-style-type: none"> • Normal free light chain ratio, • Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence (confirmation with repeat bone marrow biopsy not needed). (Presence and/or absence of clonal cells is based upon the κ/λ ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting the presence of an abnormal clone is κ/λ of $> 4:1$ or $< 1:2$.) <p>sCR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy sCR requirements.</p>
<p>Complete Remission (CR)</p>	<p>A treatment response where all of the following criteria are met:</p> <ul style="list-style-type: none"> • Negative immunofixation on serum and urine samples • Disappearance of any soft tissue plasmacytomas • $< 5\%$ plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed) <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p style="text-align: center;">NOTE: CR Requirements</p> <p>For recipients with light chain only myeloma, all of the following criteria must be met:</p> <ul style="list-style-type: none"> • Normal serum free light chain ratio • Negative immunofixation on urine samples • Disappearance of any soft tissue plasmacytomas • $< 5\%$ plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed) <p>For recipients with non-secretory myeloma, all of the following criteria must be met:</p> <ul style="list-style-type: none"> • Disappearance of all soft tissue plasmacytomas • $< 5\%$ plasma cells in the bone marrow (confirmation with repeat bone marrow biopsy not needed) </div>

<p>Complete Remission (CR) (cont.)</p>	<p>CR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy CR requirements.</p>
<p>Very Good Partial Response (VGPR)</p>	<p>One or more of the following must be present:</p> <ul style="list-style-type: none"> • Serum and urine M-protein detectable by immunofixation but not on electrophoresis • $\geq 90\%$ reduction in serum M-protein and urine M-protein level < 100 mg/24 hours. <p>VGPR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy VGPR requirements.</p>
<p>Partial Response (PR)</p>	<p>Both of the following must be present:</p> <ul style="list-style-type: none"> • $\geq 50\%$ reduction in serum M-protein • Reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg/24 hours. <p>If the serum and urine M-protein are not measurable (i.e., do not meet the following criteria):</p> <ul style="list-style-type: none"> • serum M-protein ≥ 1 g/dL, • urine M-protein ≥ 200 mg/24 hours; <p>then a $\geq 50\%$ decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria (provided the serum free light chain assay shows involved level > 10 mg/dL and the serum free light chain is abnormal).</p> <p>If serum and urine M-protein <i>and</i> serum-free light assay are not measurable, a $\geq 50\%$ reduction in bone marrow plasma cells is required in place of M-protein, provided the baseline bone marrow plasma cell percentage was $\geq 30\%$.</p> <p>In addition to the above listed criteria, a $\geq 50\%$ reduction in the size of soft tissue plasmacytomas is also required, if present at baseline.</p> <p>PR requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy PR requirements.</p>

Stable Disease (SD)	<p>Does not meet the criteria for CR, VGPR, PR, or PD.</p> <p>SD requires two consecutive assessments (of the same method) made at any time before the institution of any new therapy. If radiographic studies were performed, there must be no known evidence of progressive or new bone lesions. Radiographic studies are not required to satisfy SD requirements.</p>
Progressive Disease (PD)	<p>Requires one or more of the following:</p> <p>Increase of $\geq 25\%$ from the lowest response value achieved in:</p> <ul style="list-style-type: none"> • Serum M-component with an absolute increase ≥ 0.5 g/dL (for progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient if the starting M-component is ≥ 5 g/dL); and/or • Urine M-component with an absolute increase ≥ 200 mg/24 hours; and/or • For recipients without measurable serum and urine M-protein levels, the difference between involved and uninvolved free light chain levels with an absolute increase > 10 mg/dL; and/or • Bone marrow plasma cell percentage with absolute percentage $\geq 10\%$; and/or • Definite development of new bone lesions or soft tissue plasmacytomas, or definite increase in the size of any existing bone lesions or soft tissue plasmacytomas; and/or • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol) that can be attributed solely to the plasma cell proliferative disorder. <p>PD requires two consecutive assessments (of the same method) made at any time before classification as disease progression, and/or the institution of any new therapy.</p>
Relapse from CR (untreated)	<p>Requires one or more of the following:</p> <ul style="list-style-type: none"> • Reappearance of serum or urine M-protein by immunofixation or electrophoresis; and/or • Development of $\geq 5\%$ plasma cells in the bone marrow (relapse from CR has a 5% cutoff vs. 10% for other categories); and/or • Appearance of any other sign of progression (e.g., new plasmacytoma, lytic bone lesion, hypercalcemia). <p>Relapse requires two consecutive assessments (of the same method) made at any time before classification as relapse, and/or the institution of any new therapy.</p>

At any response level, if some but not all criteria met, the disease status should be downgraded to next lower level of response.

The percentage of plasma cells in the bone marrow aspirate and/or biopsy may also be identified on a flow cytometry report. A flow cytometry report may **NOT** be used to confirm CR (e.g., < 5% plasma cells in the bone marrow).

For more information on determining how to report disease status prior to the preparative regimen, see [Appendix V](#) and [Appendix W](#).

Example A: A 62 year old man is diagnosed with IgG Kappa multiple myeloma. He receives initial therapy with 6 cycles of bortezomib and lenalidomide/dexamethasone; and achieves a very good partial response (VGPR). The values used to determine disease status at transplant are the values obtained at diagnosis.

Time Point	BMBX	SPEP	SIFE	UPEP	UIFE	Skeletal Survey	Treatment	Disease Status
10/31/2008	27% plasma cells	3.3 g/dL	+	336 mg/24 hours	+	Negative	Bortezomib/lenalidomide/dex	Diagnosis: IgG Kappa
4/3/2009	3% plasma cells							
4/17/2009		Negative	+	Negative	Negative			VGPR
5/13/2009		Negative	+	Negative	Negative			VGPR (confirmatory)
5/17/2009							Autologous HSCT	

Example B: A 59 year old woman is diagnosed with IgA Lambda multiple myeloma. She receives bortezomib and thalidomide/dexamethasone as initial treatment and achieves a CR. A few months later she has evidence of relapse. She is then treated with lenalidomide/dexamethasone and achieves a PR. The patient receives high-dose cyclophosphamide as part of an autologous stem cell harvest. The values used to determine disease status at transplant would be the values obtained at the time of relapse.

Time Point	BMBX	SPEP	SIFE	UPEP	UIFE	Skeletal Survey	Treatment	Disease Status
01/27/2010		4.5 g/dL	+	Negative	Negative			
02/01/2010	Aspirate =18% plasma cells; biopsy=sheets of plasma cells							Diagnosis: IgA lambda

Time Point	BMBX	SPEP	SIFE	UPEP	UIFE	Skeletal Survey	Treatment	Disease Status
02/05/2010						Negative	Bortezomib/ thalidomide/d ex	
03/05/2010		2.6 g/dL	+					
4/5/2010		1.7 g/dL	+					
5/5/2010		0.5 g/dL	+					
6/4/2010		0.03 g/dL	+	Negative	Negative			
8/18/2010	1% plasma cells	0.01 g/dl	+					
9/15/2010		Not detected	+					
10/15/2010		Not detected	Negativ e					CR
11/15/2010		Not detected	Negativ e				(no treatment given)	CR (confirmatory)
12/15/2011		Not detected	Negativ e					
1/15/2011		1.9 g/dL	+	Negative	Negative			Relapse
2/15/2011	7% plasma cells	2.2 g/dL	+			Negative	lenalidomide/ dexamethaso ne	Relapse (confirmatory)
3/15/3011		1.4 g/dL	+					
4/15/2011		0.9 g/dL	+					PR
5/15/2011		0.7 g/dL	+					PR (confirmatory)
6/15/2011	3% plasma cells	0.5 g/dL	+					
7/31/2011							Autologous HSCT	

Question 182: Specify the date of the most recent assessment for disease status prior to the preparative regimen

Enter the date of the most recent assessment of disease status prior to the start of the preparative regimen. Report the date the blood/urine was collected for the laboratory evaluations (e.g., SPEP/UPEP, serum/urine immunofixation) or report the date the bone marrow was collected for pathological evaluation. A PET scan may be used **if** a previous PET scan had been obtained and **only** in limited circumstances (e.g., plasmacytomas, lytic lesions).

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

Question 183: Signed

The person completing the form must sign the form, print his/her name, and provide a phone number, fax number, and e-mail address where he/she can be reached.