Appendix B: Glossary of Terms

General Terms

absolute neutrophil count (ANC)
Neutrophils are a type of white blood cell that helps protect the body from infection. The number of neutrophils in a recipient's blood is used to track recovery after chemotherapy or HSCT. In some types of HSCT, the number of neutrophils is a marker of engraftment.

allele
One of the different forms of a gene that can occur at a single spot on a chromosome. A part of DNA representing a gene inherited from each parent to make a pair.

allele code
The NMDP uses allele codes to report the HLA allele combinations used to match recipients and donors. The codes reduce multiple allele combinations into an alphabetic term.

allogeneic hematopoietic cell transplant
Any cord blood, bone marrow or peripheral blood stem cell transplant that uses cells from a person other than the recipient. The donated cells can come from a family member or a donor who is not related to the recipient.

antibody
A protein in the blood that is created by the immune system in response to foreign substances like viruses, bacteria or tumor antigens. Each antibody recognizes a specific antigen unique to its target.

antigens
Substances capable of activating the immune system. Antigens include toxins, bacteria, foreign blood cells, and the cells of transplanted organs. Proteins found on most cells of the body are antigenic and therefore are the targets for graft-versus-host disease and graft rejection.

apheresis
A procedure where blood is taken from a person's arm and passed through a machine. The machine separates and collects certain cells such as blood-forming cells, white blood cells or platelets. The rest of the blood is returned through the other arm.

autologous hematopoietic cell transplant
A transplant using blood-forming cells collected from the recipient. The recipient's own blood-forming cells are collected, stored and then returned to the body after the recipient receives high doses of chemotherapy and/or radiation therapy. The cells are generally collected when the recipient is in remission to minimize cancer cell contamination.

blast phase
The advanced stage of chronic myelogenous leukemia or chronic lymphocytic leukemia when the number of

abnormal white blood cells in the bone marrow and blood is very high.

cellular transplantation, cellular transplant therapy
The process of replacing or supplementing a recipient's diseased blood and immune system with healthy, blood-forming, immune or other hematopoietic-derived cells collected from marrow, peripheral blood or cord blood. This may include, but is not limited to, an infusion of donor lymphocytes or mesenchymal stem cells.

chemotherapy
A drug treatment that kills cancer cells. Used to prepare recipients for a marrow, PBSC, or cord blood transplant.

confirmatory test (CT)
An additional test designed to detect only a targeted substance (i.e., virus, protein, DNA, antibody, etc.) with high specificity and low sensitivity; generally done to confirm disease after a positive screening test, as it is more costly and time consuming than a screening test.

contact date
In order for a form (Pre-, Post-TED, and/or Comprehensive Report Form) to be entered into the database, the contact date must be at least a day greater than the contact date of the previous form. If the center has not had contact with the recipient since the contact date that was reported on the previous form, a Lost to Follow-up (Form 2802) should be submitted instead.

cord blood unit (CBU)
Cord blood that meets eligibility requirements and has been typed and stored for potential transplantation.

cryopreservation
A procedure for storing tissues or blood products at extremely low temperatures.

cytomegalovirus (CMV)
A virus that can cause pneumonia, gastroenteritis or urinary tract infection in people with weakened immune systems. Many healthy people infected with the virus have no signs of infection. CMV infection is a concern because of the risk of infection to people with weakened immune systems, such as transplant recipients and those with HIV.

disease
An abnormal condition of an organism that impairs bodily functions and can be deadly. Also defined as a way of the body harming itself in an abnormal way, associated with specific symptoms and signs.

disease specific forms
Previously called "inserts" by both the Minneapolis and Milwaukee campuses of the CIBMTR. These forms are due once the primary Comprehensive Report Form (i.e., Form 2000, 2100, 2200 or 2300) is complete.

DNA repository
A facility that stores NMDP volunteer donor blood samples for HLA testing. Blood samples are either frozen or spotted on filter paper cards for later DNA-based HLA typing.

engraftment
The stage when the transplanted blood-forming cells start to grow and make healthy new blood cells derived from the donor (including autologous).

enzyme immunoassay (EIA)
See ELISA

enzyme-linked immunosorbent assay (ELISA)
A biochemical technique used to detect the presence of specific substances such as antibodies or antigens. Because it can be performed to evaluate either the presence of antigen or the presence of antibody in a sample, it is a useful tool both for determining serum antibody concentrations (such as with the HIV or hepatitis) and also for detecting the presence of antigen.

false positive
Reactive test result not due to the presence of the substance being tested but rather to an interfering or cross-reacting substance; confirmatory testing is necessary to differentiate true positive from false positive.

filgrastim
A man-made version of a normal human protein that increases the number of blood-forming cells in the body. Filgrastim is used to treat neutropenia (a low number or neutrophils), stimulate the bone marrow to increase production of neutrophils. Filgrastim is also given to donors who have agreed to donate peripheral blood stem cells (PBSC). Filgrastim is also known as G-CSF (granulocyte-colony stimulating factor) or by the trade name Neupogen®.

good clinical practices (GCP)
An international ethical and scientific quality standard for designing, conducting, recording, and reporting, trials that involve the participation of human subjects.

graft
Tissue or organ transplanted from a donor to a recipient. In some cases the recipient can be both donor and recipient.

graft failure
When transplanted blood-forming cells fail to make enough white blood cells, platelets and red blood cells. There are several causes for graft failure, including graft rejection. Failure to engraft occurs when there is no recovery of donor (or autologous) stem cell function following the HSCT, and may be caused by inadequate numbers of blood-forming cells at the time of transplantation.

graft-versus-host disease (GVHD)
A condition where the transplanted marrow or blood stem cells react against the recipient's tissues. GVHD is caused by the donor's T cells. There are two types of GVHD, acute GVHD (aGVHD) and chronic GVHD (cGVHD). GVHD can be mild or serious and is sometimes life threatening. Recipients are given immunosuppressive medication after transplant to prevent and control GVHD.

growth factor

A substance that affects cellular growth, proliferation and cellular differentiation. Cytokines and hormones are examples of growth factors that bind to specific receptors on the surface of their target cells. Growth factors often promote cell differentiation and maturation. Filgrastim is one type of growth factor.

HLA (human leukocyte antigen)
The name of the major histocompatibility complex (MHC) in humans. The superlocus contains a large number of genes related to immune system function in humans. This group of genes resides on chromosome 6 and encodes cell-surface antigen-presenting proteins and many other genes. The proteins encoded by certain genes are also known as antigens, as a result of their historic discovery as factors in organ transplantations. The major HLA antigens are essential elements in immune function.

Different classes have different functions:

HLA class I antigens (A, B & C) present peptides from inside the cell (including viral peptides if present). These peptides are produced from digested proteins that are broken down in the lysozomes. The peptides are generally small polymers, about 9 amino acids in length. Foreign antigens attract killer T-cells (also called CD8 positive cells) that destroy cells.

HLA class II antigens (DR, DP, & DQ) present antigens from outside of the cell to T-lymphocytes. These particular antigens stimulate T-helper cells to reproduce and these T-helper cells then stimulate antibody producing B-cells, self-antigens are suppressed by suppressor T-cells.

HLA testing is used to match recipients and donors for marrow, blood stem cell and organ transplants.

human T-cell lymphotropic virus (HTLV)
A single-stranded RNA retrovirus that causes T-cell leukemia and T-cell lymphoma in adults and may also be involved in certain demyelinating diseases.

immuniobiology
The study of the immune response and the biological aspects of immunity to disease.

indeterminate
Test results that do not meet criteria for either positive or negative; may require repeat or additional testing.

infectious disease markers (IDMs)
Proteins in the blood that show if a person has had an infectious disease that could be transferred to a recipient through a marrow or PBSC transplant.

informed consent
The process by which a person receives an explanation of the risks and benefits of a medical treatment or research study. If a person agrees to participate, he or she must indicate in writing that they understand and agree to the information provided. A person can provide informed consent at the age of 18.

institutional review board (IRB)
An IRB is an administrative body established to protect the rights and welfare of human research subjects

recruited to participate in research activities conducted under the auspices of the institution with which it is affiliated. The IRB has the authority to approve, require modifications in, or disapprove all research activities that fall within its jurisdiction as specified by both the federal regulations and local institutional policy.

neutralization test
A test that determines the power of an antiserum or other substance by testing its action on the pathogenic properties of a microorganism, virus, bacteria, or toxic substance.

non-myeloablative transplant
A type of transplant that uses lower doses of chemotherapy and /or radiation to prepare a recipient for transplant. In this type of preparative regimen, the recipient's hematopoietic system is not expected to be completely destroyed.

nucleic acid amplification test (NAT/NAAT)
A test can detect evidence of infection by amplifying nucleic acid in a virus, allowing for early detection of minute quantities of viral genes in the blood. The NAT can detect disease at an earlier stage than antibody testing (e.g. ELISA) since the appearance of antibodies and antigens take time to be detectable. Also see: PCR.

polymerase chain reaction (PCR)
A method of NAT testing, PCR is a powerful method for amplifying specific DNA/RNA segments and is used in the diagnosis of both infections and genetic diseases.

radiation therapy
Treatment with high-energy rays used to destroy or shrink cancer cells, or suppress the immune system.

recombinant immunoblot assay (RIBA)
A confirmatory test for hepatitis C, RIBA can detect whether a positive anti-HCV test is due to exposure to HCV (positive RIBA) or represents a false signal (negative RIBA).

research sample repository
A facility operated by the NMDP that stores research blood samples collected from marrow, PBSC donors, cord blood units, and recipients whose transplants were facilitated through the NMDP. The research samples are used in studies designed to improve outcomes for future transplant recipients.

screening test
An inexpensive, easy and rapidly performed test with high sensitivity and low specificity; used with the intention of detecting early evidence of disease.

sensitivity
A measure of how well a test correctly identifies everyone who has a disease or condition; the proportion of individuals with a disease or condition that will have a positive test.

seroconversion
The development of detectable antibodies in the blood as a result of exposure to an infectious agent.

serology
The scientific study that tests the blood serum for antibodies. Prior to seroconversion, the blood tests seronegative for the antibody; after seroconversion, the blood tests seropositive for the antibody.

specificity
A measure of how well a test eliminates everyone who does not have a disease or condition; the proportion of individuals without a disease or condition that will have a negative test.

western blot
An immunoassay technique used to detect specific proteins in blood or tissue. Western blot is used as the confirmatory HIV test. A western blot is also used to detect other diseases such as bovine spongiform encephalopathy and Lyme disease.

window period
Time between infection with a virus and the time the immune system has produced enough antibodies for the antibody test to detect. This time period can vary from person to person.

Manual Updates:
Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for any of the appendices, please reference the retired appendix on the Retired Forms Manuals webpage.

Date	Manual Section	Add/Remove/Modify	Description

Last modified: Jun 30, 2017

Appendix C: Cytogenetics

Appendix C provides and overview of cytogenetics, using cytogenetics to assess donor chimerism, and using the ISCN Functionality in FormsNet3^{SM}. Review the sections below for additional information.

Links to Sections

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

Date	Manual Section	Add/ Remove/ Modify	Description
1/24/ 2025	Appendix C: Cytogenetics	Add	Chimerism Methods of Assessment section and Table 1. Chimerism Methods added to Chimerism and Cytogenetics section
7/26/ 2024	Appendix C: Cytogenetics	Add	Information added to clarify additional forms have the ISCN functionality enabled as of 12/8/2023
4/4/ 2024	Appendix C: Cytogenetics	Add	The Reporting Other FISH Results section added to the FISH subsection
4/4/ 2024	Appendix C: Cytogenetics	Add	The Reporting Other Karyotype Results section added to the Karyotype subsection
7/28/ 2023	Appendix C: Cytogenetics	Add	Version 3 of Appendix C: Cytogenetics released with the Summer 2023 Quarterly release

Last modified: Jan 27, 2025

Cytogenetic Assessments

Introduction to Cytogenetics

Cytogenetic analysis is the study of chromosomes. Cytogenetic assessment involves testing a sample of cells for the presence of chromosomal abnormalities. Cytogenetic assessment can also be done to determine chimerism following an allogeneic infusion when there is a sex mismatch between the donor and recipient. Specific methods of assessment include karyotyping and fluorescence in situ hybridization (FISH).

This section will provide information on the two methods of assessment captured on the CIBMTR forms: Karyotyping and FISH

Links to Sections

Karyotyping
FISH (Fluorescence in situ hybridization

Section Updates:

Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
4/4/ 2024	Add	The Reporting Other FISH Results section added to the FISH subsection	Added for clarification
4/4/ 2024	Add	The Reporting Other Karyotype Results section added to the Karyotype subsection	Added for clarification
7/28/ 2023	Add	Appendix C: Cytogenetics re-vamped. The original 'Introduction to Chromosomes,' and 'Cytogenetic Assessment Methods,' previously listed in version 2 of Appendix C is now separated into its own combined subsection and re-vamped in version 3 of Appendix C	Added with release of ISCN Functionality in the Summer 2023 release

Last modified: Apr 04, 2024

Karyotyping

Karyotyping, also referred to as conventional cytogenetics, is performed by culturing cells (growing cells under controlled conditions) until they reach the dividing phase. Techniques are performed to visualize chromosomes during cell division so various bands and reconfigurations are seen. Karyotype assessments typically examine around 20 cells. Figure 1 below shows an example of a karyotype. The chromosomes are arranged in numerical order with sex chromosomes included last.

Figure 1. Karyotype

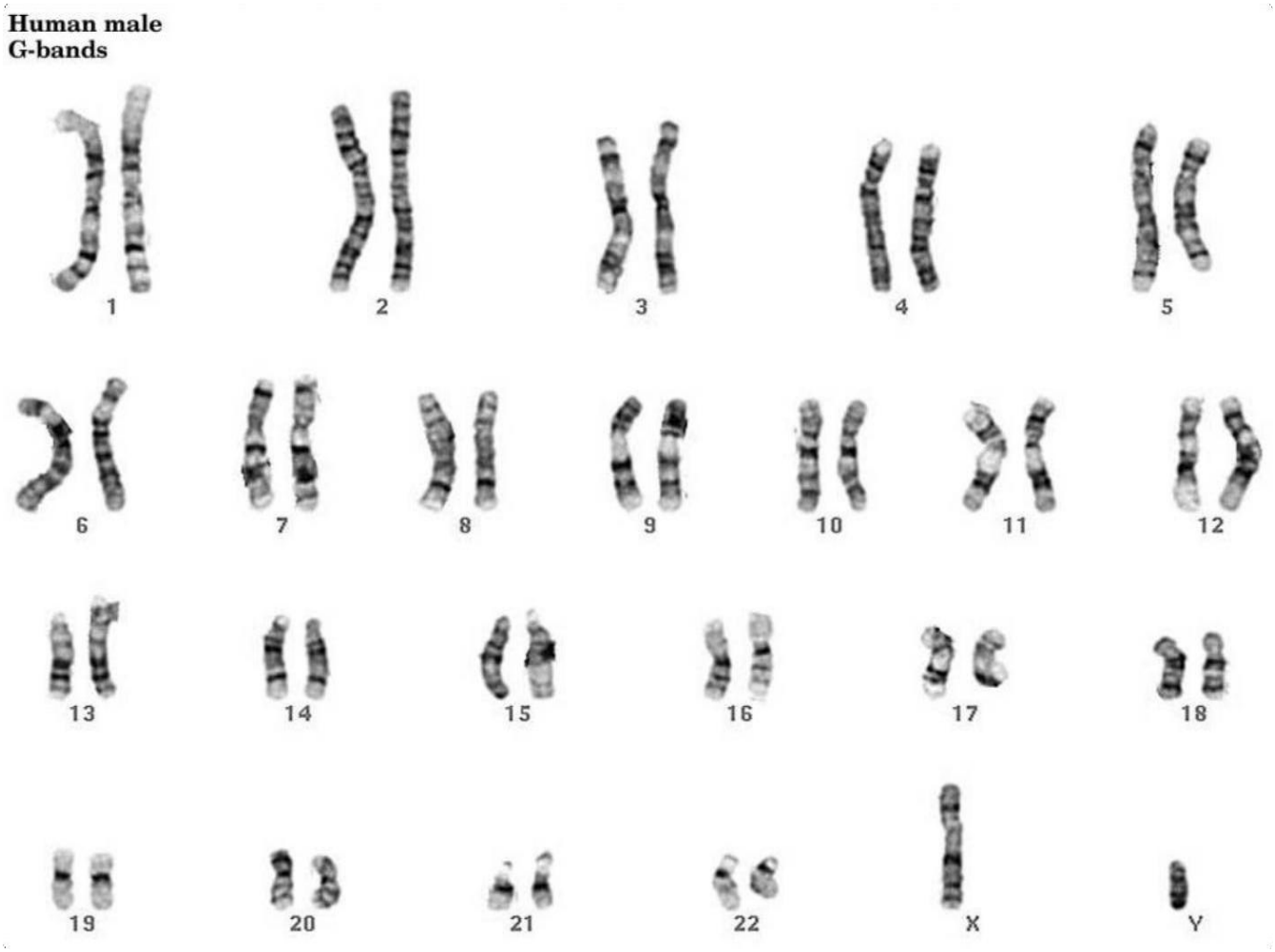


Image source: Department of Pathology. Cytogenetics Gallery, University of Washington, www.pathology.washington.edu/galleries/cytogallery/main.php?file.

Introduction to Chromosomes

Typical human cells contain 23 chromosome pairs (46 total chromosomes)

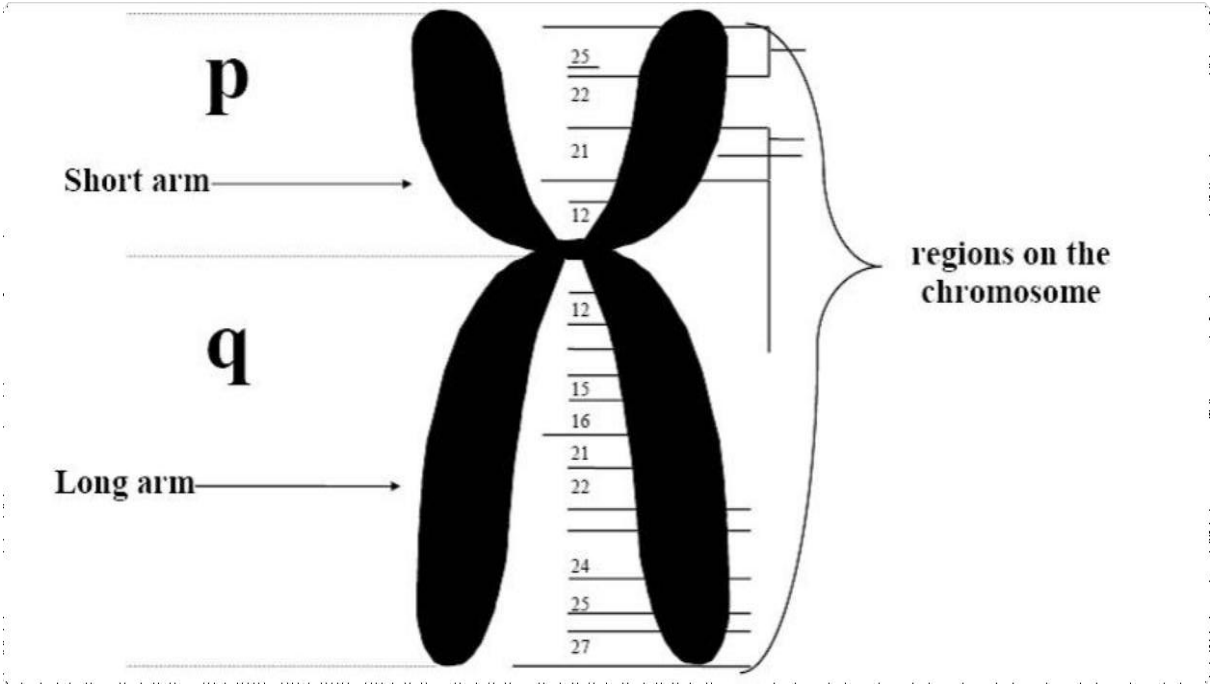
- 22 of these pairs are autosomal (non-sex) chromosomes
    - Each autosomal chromosome is referred to by its number, one through 22

- The remaining two chromosomes (the 23rd pair) are referred to as sex chromosomes
    - Identified by either X (female) or Y (male)
    - Females have two X chromosomes while males have one X and one Y chromosome

Karyotype Abnormalities

Karyotype results are provided in a unique format which is demonstrated in Figure 3 below. Karyotype abnormalities are described by identifying the involved chromosomes and specific locations, when applicable. The location is noted when an abnormality involves only a specific section of a chromosome or when a translocation has occurred. The location is defined by two pieces of information, the chromosome arm and the arm region. The arm refers to the short (p arm) or long (q arm) end of the chromosome on opposite sides of the centromere. The arm region describes the distance from the centromere. See Figure 2 below for a depiction of the chromosome arm and arm regions.

Figure 2. Chromosome Structure



Chromosomal abnormalities refer to changes in the amount or location of chromosomal material. A basic knowledge of chromosome symbols / abbreviations is required to interpret karyotype test results. Definitions of general categories of chromosomal abnormalities are provided below. Definitions of common cytogenetic symbols / abbreviations are provided in Table 1.

- **Addition**: Extra chromosomal material is present. This includes extra material within a specific region of a chromosome and entire extra chromosomes. Extra material is described by the location while extra whole chromosomes are described based on the quantity present. Trisomy refers to three chromosomes present (one extra) while tetrasomy refers to four chromosomes present (two extra).
- **Deletion**: Loss of chromosomal material. This includes loss of material within a specific region of a chromosome and entire missing chromosomes. Loss of material is described by location while entire missing chromosomes are described based on the quantity present. Monosomy refers to one

chromosome present (one lost) while nullisomy refers to no chromosomes present (both lost).

- **Translocation**: An exchange of chromosomal material between two or more chromosomes.
- **Inversion**: The base pair order is reversed for a specific region of a chromosome.
- **Hyperdiploidy**: The total number of chromosomes present is higher than normal. The definition of hyperdiploidy is typically further specified on the form being completed. For example, a form may require greater than 50 chromosomes be present to report hyperdiploidy.
- **Hypodiploidy**: The total number of chromosomes present is lower than normal.

Table 1. Cytogenetic Symbols and Abbreviations

Symbol / Abbreviation	Definition
[ ] (square brackets)	Surrounds number of cells within the clone
< > (angle brackets)	Surround the ploidy level
( ) (parenthesis)	Surround the altered chromosomes
/ (backslash)	Separates clones
+	Addition of an entire chromosome, also known as trisomy (i.e., +21)
-	Loss of an entire chromosome, also known as monosomy (i.e., -7)
; (semicolon)	Separates affected chromosomes in structural rearrangements involving > 1 chromosome
, (comma)	Separates chromosome numbers, including sex chromosomes, and abnormalities
c	Constitutional abnormality
der	Derivative chromosome
dic	Dicentric
dim	Diminished
dup	Duplications
idem	Stemline karyotype in a subclone
ider	Isoderivative chromosome
idic	Isodientric chromosome
inv	Inversion of chromosomal material (i.e., inv(1)(p36q21)
p	Short arm of a chromosome
p+ / add(p)	Addition of chromosomal material to the short arm of a chromosome
p- / del(p)	Loss of chromosomal material to the short arm of a chromosome
Ph+	Philadelphia chromosome, arises from translocation t(9;22)
q	Long arm of a chromosome
q+ / add(q)	Addition of chromosomal material to the long arm of a chromosome
q- / del(q)	Loss of chromosomal material to the long arm of a chromosome
t	Translocation of chromosomes (i.e., t(1;19))
X	Female sex chromosome
Y	Male sex chromosome

Interpreting Karyotype Results

In a karyotype result (see Figure 3 below), the first item noted is the total number of chromosomes, followed by a comma, and then the sex chromosomes. If the karyotype is abnormal, a comma follows the sex chromosomes, and then the abnormalities (listed as a symbol or abbreviation), each separated by a comma.

When one chromosome is altered in an abnormality, the affected chromosome is enclosed within parenthesis, immediately following the symbol indicating the alteration (i.e., del(8), inv(9)). When two more chromosomes are affected in an abnormality, a semicolon is used to separate the chromosomes (i.e., t(8;9)). To indicate additional, missing, normal, or abnormal chromosomes, a plus or minus sign is noted prior to the affected chromosome (i.e., -8, +21). A plus or minus sign noted after the chromosome arm symbol (p or q), indicates the addition or loss of chromosomal material to the specified arm. Abnormalities identified in different clones are separated by a backslash. Different clones are identified when findings are detected in some, but not all cells. The number of cells with the specified karyotype is enclosed in brackets, denoted at the end of the karyotype string.

Figure 3. Karyotype Results

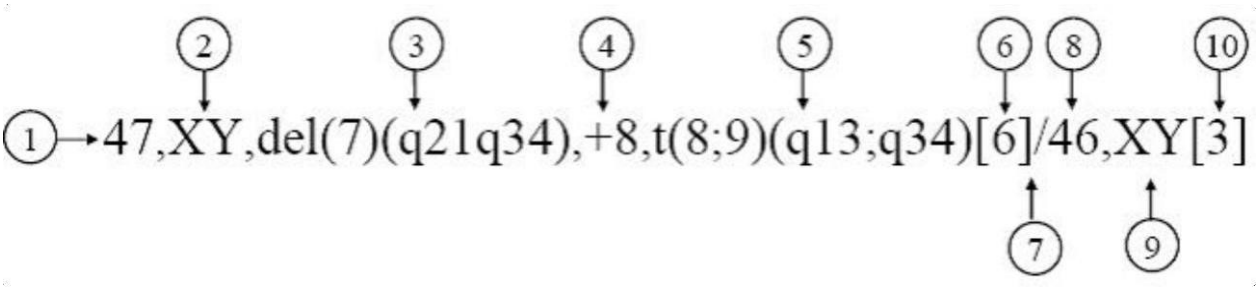


Table 2. Karyotype Results

Number	Definition
1	Number of chromosomes detected
2	Sex chromosomes
3	Deletion of chromosomal material on the long arm of chromosome 7 between regions 21 and 34
4	Trisomy 8; extra chromosome 8
5	Translocation of chromosomal material on the long arm of chromosome 8 and the long arm of chromosome 9
6	Number of cells (metaphases) examined with these abnormalities
7	Separates information about differing karyotypes
8	Number of chromosomes detected
9	Sex chromosomes
10	Number of cells examined with this normal karyotype

Clonal verses Non-Clonal and Constitutional Findings

When reporting karyotype results, a data manager must distinguish between clonal and non-clonal findings. Clonal abnormalities are present in multiple cells and indicate a separate cell line, such as a malignant population, is present. Additionally, karyotyping may also detect constitutional abnormalities. These are abnormalities present since birth. Examples include, but are not limited to, trisomy 21 and Klinefelter's syndrome. Constitutional abnormalities should not be reported.

Example 1: Karyotyping was performed at diagnosis and `46,XY,+21[20]` was detected. In this case, since only +21 was detected, **No abnormalities** should be reported as the results for karyotype obtained at diagnosis.

Reporting Other Karyotype Results

The 'other' karyotype data field is used to report abnormalities detected, but not listed as an option on the form. Abnormalities that should be reported in the 'other' specify data field, include, but are not limited to the following:

- Abnormality detected but not listed as a specific option on the form
- Tetrasomies: Four copies of a specific chromosome
    - Example: `48,XY,+21,+21[20]`
        - The '+21,+21', is not the same as '+21,' which maybe listed as an option on the form. This abnormality indicates there are four copies of chromosome 21, where as +21 indicates there are three copies
- 'Monosomy or deletion' of a specific chromosome: The entire chromosome or part of the chromosome is missing but the exact abnormality is unknown.
    - Example: 'Monosomy 7 or deletion 7' is detected
        - Report this abnormality under 'other' and specify 'Monosomy 7 or deletion 7'
- 'Trisomy or add': An extra entire chromosome or part of the chromosome but the exact abnormality is unknown.
    - Example: 'Trisomy 3 or addition 3' is detected
        - Report this abnormality under 'other' and specify 'Trisomy 3 or addition 3'
- Derivatives: A chromosome derived from a translocation
    - Example: `46,XX,der(1)t(1;12)(p22;q13)[20]`
        - This abnormality indicates one of the chromosome 1 has lost a some of the p arm from the other chromosome 1 and gained some of the q arm from chromosome 12. This is not the same as 't(1;12)' where the material from chromosome 1 and 12 swap with each other.
        - Report this abnormality under 'other' and specify 'der(1)t(1;12)'

Section Updates:

Question Number	Date of Change	Add/Remove/ Modify	Description	Reasoning (If applicable)
Reporting Other Karyotype Results	4/4/2024	Add	The Reporting Other Karyotype Results section added	Added for clarification

Last modified: Apr 04, 2024

FISH (Fluorescence in situ hybridization)

FISH is a molecular cytogenetic technique using fluorescent probes that bind to a specific part of a chromosome (i.e., the probes recognize and bind to fragments of DNA). It is a sensitive technique that can assess hundreds of cells per test. The probes are mixed with cells from the tissue sample. A fluorescent "tag" is then used to visualize the binding of the probe to the cells. Probes can identify the number of chromosomes or gene copies within a cell as well as the relative locations of specific genes or chromosome regions. Unlike karyotype assessments, FISH can be done on non-dividing, or interphase, cells. A FISH assessment typically examines between 200 and 500 cells.

Each probe has a specific target or set of targets and is therefore only capable of detecting abnormalities associated with that area. Additionally, the type of probe used affects the interpretation of the results. See Table 1 for descriptions of common categories of FISH probes.

Table 1. FISH Probes

FISH Probe	Description
Centromere Enumeration Probe (CEP)	Targets the centromere and is used to count the number of a specific chromosome in a cell (e.g., trisomy 8 or +8)
Locus Specific	Targets a single locus other than the centromere and is used to detect additions, deletions, or rearrangements
Dual Fusion	Targets two loci and is used to detect translocations
Break-apart	Used to confirm gene rearrangements. The 3' portion of the gene or region is in one color and the 5' is in another color. If rearranged, colors are separate

It is important to know what a FISH assessment is testing for before trying to interpret the results. For instance, a probe specific to the p arm of chromosome 9 would not be capable of detecting a deletion anywhere on chromosome 4. In Figure 1 below, two cells were exposed to centromere enumeration probes (CEP) specific to chromosomes 6 and 8 in order to determine the number of each chromosome present. Both cells have two copies of chromosome 6 (green probes) and three copies of chromosome 8 (red probes). This FISH result indicates the presence of a trisomy of chromosome 8.

Figure 1. FISH

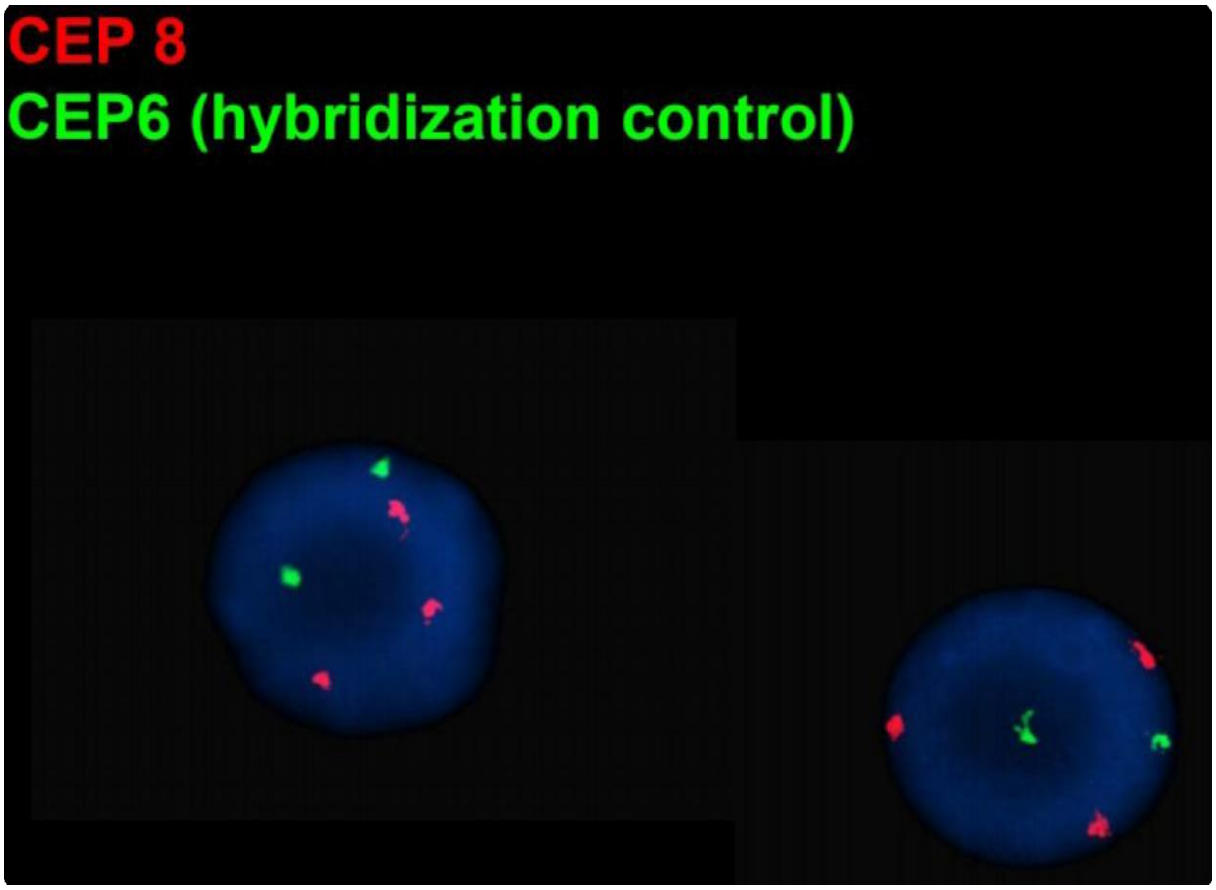


Image source: Weisdorf, Daniel J., MD. “Cytogenetics.” 2017 Clinical Research Professionals / Data Management Conference. Orlando. 21 Feb. 2017. Cibmtr.org. Web. 6 Dec. 2017.

FISH Results

FISH Results
FISH results are usually provided as a percentage or ratio of cells, for which, an abnormality was detected. The result may also be accompanied by a normal range to define when the test is considered positive for the abnormality being assessed. Additionally, the FISH ISCN nomenclature along with the interpretation / impression of the results is also commonly included. When reporting FISH results, review the interpretation / impression section of the report to determine which abnormalities are detected.

Figure 2 is an example FISH report. It includes the identity of each probe, the number of abnormal cells, the normal range, a result for each probe, the ISCN nomenclature, and a final interpretation. The report confirms the TP53 and CEP12 probes detected abnormalities; however, the TP53 probe did not detect an abnormality at a rate above the normal cut off value (7%). The final interpretation indicates these findings represent a gain of chromosome 12 (trisomy).

Figure 2. FISH Results

FLUORESCENCE *IN SITU* HYBRIDIZATION REPORT

FISH Probes*: CLL [Abbott (Vysis), Inc.]

PROBE SETS CHROMOSOME LOCI	#CELLS ANALYZED	ABNORMAL	NORMAL CUTOFF VALUE (95% CI)	RESULTS	ISCN NOMENCLATURE 2009
11q22.3 (ATM), 17p13 (TP53)	**200**	**10**	**Del 11q22.3 > 6.0% Del 17p13 > 7.0%**	**Loss of 17p13 (TP53) detected (5%) Abnormal signal pattern.**	**nuc ish(ATM, TP53x1)[10/200]**
CEP 12/ 13q14(D13S319),13q34	**200**	**130**	**Gain of 12 > 2.5% Del 13q > 5.5% Homozygous Del 13q > 1.5% Loss of 13 > 5.5%**	**Gain of CEP 12 detected (65%). Abnormal signal pattern.**	**nuc ish (D13S319x2,13q34x2,CEP12x3)[130/200]**
11q13(CCND1)/ 14q32 (IGH)	300	---	t(11;14) > 1%	No CCND1/IGH rearrangement. Normal signal pattern	nuc ish (CCND1x2),(IGHx2)
CEP6(D6Z1), 6q22-23(MYB)	300	---	Del(6q22-23) > 3%	No deletion of MYB detected. Normal signal pattern.	nuc ish(D6Z1x2,MYBx2)

* FISH only testing is not equivalent to conventional cytogenetic analysis of the patient's specimen , and is limited to the specific probe(s) and their corresponding DNA locations (genes) only.

Summary: **Abnormal CLL FISH Panel**

Final Interpretation: This fluorescence in situ hybridization (FISH) analysis showed an abnormal signal pattern with gain of chromosome 12 in 130 out of 200 (65%) cells, implying trisomy 12 consistent with CLL.

Image source: Cancer Genetics, INC. "CGI Sample Reports." Issuu. N.p., 16 Nov. 2013. Web. 11 Dec. 2017. https://issuu.com/cgi201/docs/cgi_sample_reports_booklet/37>.

FISH reports may only refer to a probe by a gene name without indicating the chromosome number / region. For example, the report in Figure 2 could have only specified an ATM probe was used without also indicating the gene location was 11q22.3. It may be necessary, depending on the CIBMTR form, to know the gene location to accurately report the test results. The laboratory performing the study is the best resource for more information about the test that was done. A probe search can also be done using the HUGO Gene Nomenclature Committee's website genenames.org. This website provides gene symbols, approved names, associated names, and chromosomal locations for many of the probes in current use.

Table 2. Common Genes with Corresponding Chromosome

Gene	Chromosome
RPN1 / MECOM	t(3;3)
DEK / NUP214	t(6;9)
KMT2A / MLLT3	t(9;11)
BCR-ABL1	t(9;22)
PML / RARA	t(15;17) and variants
CBFB / MYH11	t(16;16)
TP53	del(17p)
MLL	11q23
E2A-PBX1	t(1;19)
MLL-AFF1	t(4;11)
IL3-IGH	t(5;14)
TCRA / TCRD-TLX1	t(10;14)
TEL-AML1 (ETV6-RUNX1)	t(12;21)
ETV6-RUNX1	t(12;21)
DUX4	4q35.2
PAX5	9p13.2
NUTM1	15q14
MYC	8q24
MYC rearrangements	t(8;14), t(2;8), t(8;22)
RUNX1-RUNX1T1 (AML1-ETO)	t(8;21)

Reporting Other FISH Results

The 'other' FISH data field is used to report abnormalities detected, but not listed as an option on the form. Abnormalities that should be reported in the 'other' specify data field, include, but are not limited to the following:

- Abnormality detected but not listed as a specific option on the form
- Tetrasomies: Four copies of a specific chromosome
    - Example: FISH results detect 'tetrasomy of 9, 11, and 15'
        - This abnormality indicates there are four copies of chromosome 9, 11, and 15, which is not the same as +9, +11, or +15, indicating there are three copies of chromosome 9, 11, and 15
- 'Monosomy or deletion' of a specific chromosome: The entire chromosome or part of the chromosome is missing but the exact abnormality is unknown.
    - Example: 'Monosomy 7 or deletion 7' is detected
        - Report this abnormality under 'other' and specify 'Monosomy 7 or deletion 7'
- 'Trisomy or add': An extra entire chromosome or part of the chromosome but the exact abnormality is unknown.
    - Example: 'Trisomy 3 or addition 3' is detected
        - Report this abnormality under 'other' and specify 'Trisomy 3 or addition 3'

Section Updates:

Question Number	Date of Change	Add/Remove/ Modify	Description	Reasoning (If applicable)
Reporting Other FISH Results	4/4/2024	Add	The Reporting Other FISH Results section added	Added for clarification

Last modified: Apr 04, 2024

Chimerism and Cytogenetics

Chimerism Methods of Assessment

Various methods of assessment can be used to assess donor chimerism. Table 1 provided below lists chimerism methods and their descriptions:

Table 1. Chimerism Methods

Method	Description
Karyotyping for XX / XY	Cells grown in culture, stained, and examined under a microscope to identify the number* of cells matching the sex of the donor. This method is only valid when donor and recipient are sex mismatched.
Fluorescent in situ hybridization (FISH) for XX / XY	Cells are exposed to fluorescent DNA probes which attach to X and Y chromosomes. A microscope is used to identify the **number** of cells matching the sex donor. This method is only valid when donor and recipient are sex mismatched.
Restricted fragment length polymorphisms (RFLP)	A restriction fragment is a portion of DNA which has been cut out by an enzyme. RFLP testing beings by isolating DNA from the sample. Enzymes are used to cut the DNA at specific loci resulting in many unique restriction fragments. The fragments are separated according to size by electrophoresis. The unique pattern of separation is used to identify the **percent** donor DNA present in the sample.
Variable number tandem repeat (VNTR), micro- or minisatellite	VNTR refers to a portion of DNA containing a repeating sequence of base pairs (micro- or minisatellite). The number of times a micro- or minisatellite repeats within specific loci can differ between individuals. These differences are used to distinguish donor DNA from recipient DNA. VNTR testing involves obtaining samples from the recipient and donor prior to transplant. Specific loci are compared to determine which loci contains VNTRs unique to the donor. After transplant, DNA is isolated from recipient samples. Donor-specific VNTRs are amplified by PCR techniques. The sample is then analyzed to determine the **percent** donor DNA present.
Small tandem repeat (STR), micro-or minisatellite	STR also refers to a portion of DNA containing a repeating sequence of base pairs (micro- or minisatellite). The number of times a micro- or minisatellite repeats within specific loci can differ between individuals. These differences are used to distinguish donor DNA from recipient DNA. STR testing involves obtaining samples from the recipient and donor prior to transplant. Specific loci are compared to determine which loci contains STRs unique to the donor. After transplant, DNA is isolated from recipient samples. Donor-specific STRs are amplified by PCR techniques. The sample is then analyzed to determine the **percent** donor DNA present.
Amplified fragment	A restriction fragment is a portion of DNA which has been cut out by an enzyme. AFLP testing begins by isolating DNA from the sample. Enzymes are used to cut the DNA at specific loci

length polymorphisms (AFLP)	resulting in many unique restriction fragments. Many restrictions fragments are amplified using PCR techniques. The fragments are separated according to size by electrophoresis. The unique pattern of separation is used to identify the **percent** donor DNA present in the sample.

Cytogenetic Methods

Cytogenetic assessments can be performed to identify markers of disease, determine chimerism following an allogeneic cellular infusion, or both. Cytogenetic assessment of chimerism is usually only done for sex mismatched pairs of recipients and donors. In these cases, a karyotype or FISH study can determine the ratio of cells containing female vs. male sex chromosomes. A unique form of karyotype assessment, Q banding, can also be used to assess chimerism for sex matched recipient and donor pairs; however, molecular techniques involving PCR amplification are much more common.

Disease assessment by cytogenetic methods involves the identification of disease-specific markers (e.g., -7, del(5q), Philadelphia chromosome). Once a marker is identified, cytogenetic assessments can be repeated to determine whether the marker, and therefore the disease, is still detectable. The types of markers identified can affect the disease classification and inform the treatment plan. A cytogenetic assessment cannot be considered a disease assessment until this method has detected a marker of disease. In other words, if cytogenetic studies have always been negative, the recipient's disease is not considered to be assessed by this method because there are no known cytogenetic abnormalities to evaluate.

CIBMTR forms generally capture chimerism data separately from disease assessment data. Therefore, it is important to know what information can be reported based on the assessment performed.

Example 1: Consider a recipient of an allogeneic product obtained from a sex mismatched donor as part of treatment for AML. The cytogenetic abnormality t(8;21) was identified as a marker of this recipient's disease on previous cytogenetic assessments. Would the following cytogenetic assessments be reported in chimerism data fields, disease assessment data fields, or both?

- Karyotype: Report this assessment in both chimerism and disease assessment data fields. A karyotype is capable of detecting autosomal and sex chromosomes. The test would confirm whether the t(8;21) abnormality was still present and also provide a ratio of female to male cells.
- FISH [X / Y probe(s) only]: Only report this assessment in chimerism data fields. The probes are able to provide a ratio of female to male cells, but are not capable of detecting the t(8;21) abnormality.
- FISH [t(8;21) probes only]: Only report this assessment in disease assessment data fields. The probes are able to detect the t(8;21) abnormality, but are not capable of providing a ratio of female to male cells.
- FISH [X / Y probe(s) and t(8;21) break apart probe]: Report this assessment in both chimerism and disease assessment data fields. The X / Y probe(s) will provide chimerism data while the t(8;21) probe results will be captured as a disease assessment.

Section Updates:

Date of	Add/	Description	Reasoning (If

Change	Remove/ Modify		applicable)
1/24/ 2025	Add	Chimerism Methods of Assessment section and Table 1. Chimerism Methods added	Added for clarity
7/28/ 2023	Add	Appendix C: Cytogenetics re-vamped. The original ‘Chimerism and Disease Assessments’ previously listed in version 2 of Appendix C is now separated into its own subsection in version 3 of Appendix C	Added with release of ISCN Functionality in the Summer 2023 release

Last modified: Jan 27, 2025

ISCN Functionality

Reporting the International System of Human Cytogenetic Nomenclature (ISCN) Compatible String in FormsNet3^{SM}

CIBMTR is licensing a software program developed by Washington University School of Medicine in St. Louis, called CytoGenetic Pattern Sleuth (CytoGPS) to validate the International System of Human Cytogenetic Nomenclature (ISCN) compatible string data field. This program utilizes the 2016 edition of the International System of Human Cytogenomic Nomenclature (ISCN 2016).

As of July 28, 2023, the International System of Human Cytogenetic Nomenclature (ISCN) compatible string is enabled for karyotyping on the Disease Classification (2402) Form for AML, ALL, MDS, MPN, and PCD. As of December 8, 2023, this data field is also enabled for the following disease-specific forms:

- MDS Pre-Infusion (2014) and MDS Post-Infusion (2114) Forms
- PCD Pre-Infusion (2016) Form
- Aplastic Anemia Pre-Infusion (2028) and Aplastic Anemia Post-Infusion (2128) Forms
- MPN Pre-Infusion (2057) and MPN Post-Infusion (2157) Forms

This data field is not enabled for FISH.

Depending on the lab used, karyotype results may not be structured using the ISCN nomenclature. Additionally, karyotype results may have an error or typo, causing the karyotype string to not be valid within ISCN nomenclature.

Review the sections below for information on to use the ISCN functionality, common errors, and how to resolve them.

Links to Sections

Section Updates:

Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
7/26/ 2024	Add	Information added to clarify additional forms have the ISCN functionality enabled as of 12/8/2023	Added for clarification
7/28/	Add	Appendix C: Cytogenetics re-vamped. ISCN	Added with release of ISCN

2023		Functionality added with version 3 of Appendix C	Functionality in the Summer 2023 release

Last modified: Jul 29, 2024

Entering ISCN Compatible String

Valid ISCN Compatible String

Depending on the lab used, karyotype results may not be structured using the ISCN nomenclature. Additionally, karyotype results may have an error or typo, causing the karyotype string to not be valid within ISCN nomenclature.

For the karyotype to be a 'valid' ISCN compatible string, the karyotype results should contain the following:

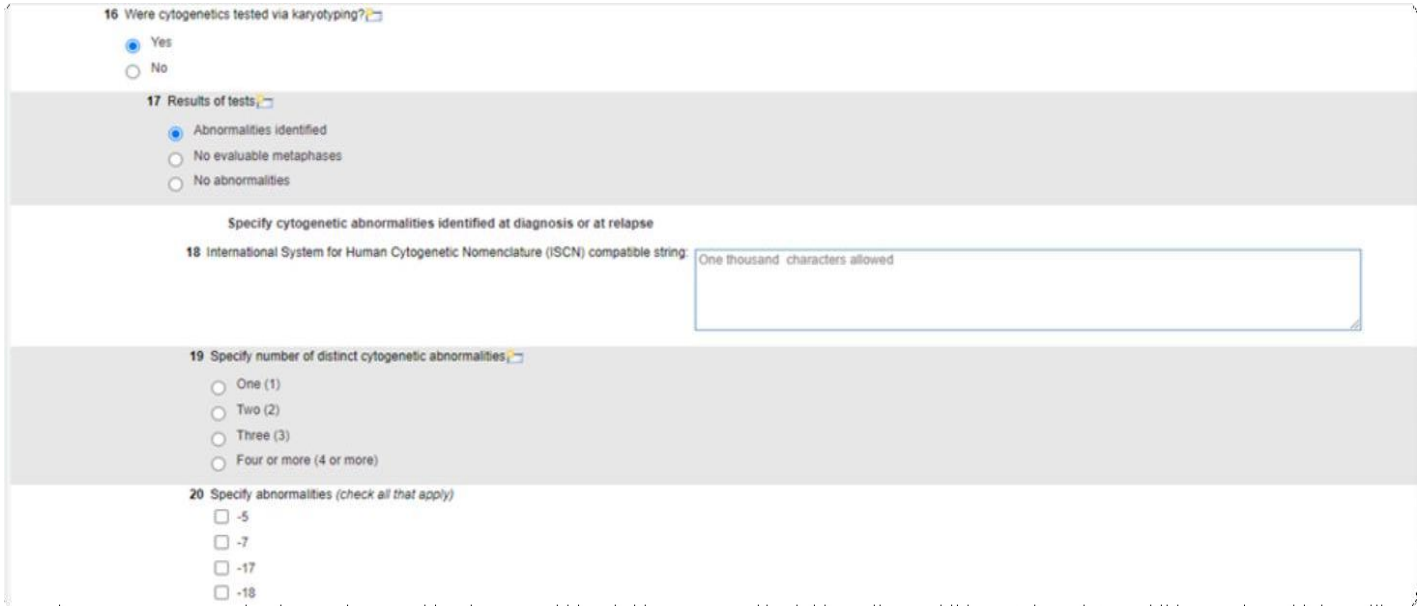
- The total number of chromosomes detected
- Sex chromosomes
- Abnormalities are denoted by a symbol or an abbreviation
- Each abnormality separated by a comma
- Parenthesis included when each abnormality specifies the location of the anomaly on the chromosome
    - The parenthesis should include an 'open' and 'closed' parenthesis
- The number of cells with abnormalities, enclosed in brackets
    - The brackets should include an 'open' and 'closed' bracket
- Spacing
    - When a symbol or abbreviation immediately precedes or follows a parenthesis, a space is not used (i.e., `47,XY,del(7)(q21q34),+8,t(8;9)(q13;q34)[20]`)
    - When > 1 symbol or abbreviation is used together, each symbol / abbreviation is separated by spaces (i.e., psu dic)
    - When the symbol or abbreviation is before the total number of sex chromosomes and parenthesis are not present, a space is used to separate the symbol / abbreviation from the number of sex chromosomes (i.e., `mos 47,XXX[20]`)

Entering the ISCN Compatible String in FormsNet3^{SM}

If karyotyping was performed the following questions will always be answered, regardless of the results:

- Were cytogenetics tested via karyotype *and*
- Results of test

Image 1. Questions always answered



The question *Were cytogenetics tested via karyotype* and *Results of test* will always be answered regardless of if the ISCN compatible string is entered or if the number of abnormalities and the specific abnormalities are reported

If karyotyping was performed and abnormalities were identified, then either of the following must be completed:

- The International System of Human Cytogenetic Nomenclature (ISCN) compatible string *or*
- The number of abnormalities identified, along with the specific abnormalities must be reported

If the ISCN compatible string is entered in FormsNet3^{SM}, the number of abnormalities detected, and specific abnormalities identified data fields will be disabled in the system.

Image 2. Disabling of data fields

> **Complex ISCN Strings**
> The more complex the ISCN string is, the longer the time it will take for FormsNet3^{SM} to process the string (processing may take up to 45 seconds).

Use the following steps to enter the ISCN compatible string

- Copy the karyotype result from the karyotype report and paste into the ISCN compatible string data field. If the source karyotype document does not allow copy/paste, the ISCN string needs to be typed into the ISCN compatible string data field.
  - The karyotype result entered must be a valid ISCN compatible string
- If the karyotype results are considered invalid, a FormsNet3^{SM} error will occur, and the entered karyotype result must be corrected
  - The FormsNet3^{SM} error cannot be overridden
  - Review Common Errors section below for an overview of common errors and corrections
- If FormsNet3^{SM} error cannot be corrected, then remove the data entered in the ISCN compatible string data field, and select the number of abnormalities identified and the specific abnormalities detected

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Feb 12, 2024

Common Errors

Listed in Table 1 are common typographical errors. If a FormsNet3^{SM} error arises after entering the ISCN string, review Table 1 to determine how to correct the error. Seek physician clarification as needed. If unable to correct the error, remove the ISCN string entered in FormsNet3^{SM} and select the applicable abnormalities listed.

Table 1. ISCN Compatible String Errors and Corrections

Error	Correction	Example
Parenthesis encloses the total number of cells with abnormalities	Update the parentheses to brackets	Error: 46,XX(20) Correct: 46,XX[20]
Brackets enclose the altered chromosome in an abnormality	Update the brackets to parentheses	Error: 46,XY,del[17p][20] Correct: 46,XY,del(17p)[20]
A colon is used to separate two more chromosomes affected in an abnormality	Update the colon to a semicolon	Error: 46,XY,t(9:22)[20] Correct: 46,XY,t(9;22)[20]
A comma is used to separate two more chromosomes affected in an abnormality	Update the comma to a semicolon	Error 46,XY,t(9,22)[20] Correct: 46,XY,t(9;22)[20]
A period is used to separate two more chromosomes affected in an abnormality	Update the period to a semicolon	Error: 46,XY,t(9.22)[20] Correct: 46,XY,t(9;22)[20]
A period is used to separate multiple abnormalities identified	Update the period to a comma	Error: 46.XX.-7.+8[20] Correct: 46,XX,-7,+8[20]
A semicolon is used to separate different clones	Update semicolon to a backslash	Error: 45,XY-7[15];46,XY[5] Correct: 45,XY-7[15]/46,XY[5]
A comma is used to separate different clones	Update comma to a backslash	Error: 45,XY-7[15],46,XY[5] Correct: 45,XY-7[15]/46,XY[5]
A period is used to separate different clones	Update period to a backslash	Error: 45,XY-7[15].46,XY[5] Correct: 45,XY-7[15]/46,XY[5]
Parenthesis, brackets, commas, and / or backslashes are missing	Update results to include missing symbol	Error: 46XX,del17p[15]46,XX[5 Correct: 46,XX,del(17p)[15]/46,XX[5]
Sex chromosomes are missing	Update results to include sex chromosomes	Error: 47,+8[20] Correct: 47,XY,+8[20]
Total number of chromosomes are missing	Update results to include missing number of chromosomes	Error: XX,[20] Correct: 46,XX[20]
Total number of cells with missing	Update results to include missing number of cells	Error: 46,XX Correct: 46,XX[20]

Section Updates:

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

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Last modified: Jul 31, 2023

Reporting at the In Between Timepoint

Depending on the disease, the 'in between' timepoint is asked to capture all cytogenetic abnormalities detected in between diagnosis and the last evaluation. When more than one karyotyping is completed in between diagnosis and the last evaluation, enter every karyotype with an abnormality in the ISCN compatible string data field, with each karyotype separated by a backslash and no spaces.

Example 1

In between diagnosis and the last evaluation, a recipient was assessed by karyotyping on four different dates.

- January 2, 2022: 46,XX,del(9q)[20]
- March 15, 2022: 46,XX,del(9q),del(17q)[12]/46,XX[8]
- June 8, 2022: 46,XX,del(9q)[20]
- July 15, 2022: 46,XX[20]

The following should be entered in the ISCN compatible string for the in between timepoint:
46,XX,del(9q)[20]/46,XX,del(9q),del(17q)[12]/46,XX[8]/46,XX,del(9q)[20]

Example 2

In between diagnosis and the last evaluation, a recipient was assessed by karyotyping on three different dates.

- January 12, 2022: 47,XY,+8,t(9;22)[20]
- April 25, 2022: 47,XY,del(7q),+8,t(9;22)[18]/46,XY[2]
- August 10, 2022: 46,XY,t(9;22)[20]

The following should be entered in the ISCN compatible string for the in between timepoint:
47,XY,+8,t(9;22)[20]/47,XY,del(7q),+8,t(9;22)[18]/46,XY[2]/46,XY,t(9;22)[20]

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jul 31, 2023

Additional Information

See below for additional information on how to enter data in the ISCN compatible string data field.

- The ISCN compatible string data field has a 1,000 character limit
- Do not report FISH results
    - If the results contain ‘nuc ish,’ do not report the results as these are considered FISH results
- The ISCN compatible string data field error cannot be overridden. If an error is fired, it must be addressed and corrected, or the field left blank and the abnormalities selected in the specific abnormalities detected section of the form
- The ISCN compatible string data field cannot be overridden
- A karyotype report alone cannot be attached
    - Either the ISCN compatible string data field or the number of abnormalities identified along with the specific abnormalities detected must be completed
    - FormsNet3^{SM} does not have the capability to extract the abnormalities from an attached report
- If only a constitutional abnormality is present, report ‘no abnormalities’
    - The ISCN compatible string and the number of abnormalities identified along with the specific abnormality data fields will not be answered
    - Example: `47,XX,+21[20]` is identified at diagnosis
        - +21 represents Down Syndrome which is a constitutional abnormality and should not be reported.
        - In this case, report **Yes**, karyotype was performed, and **No abnormalities** were detected

If there are questions on how to use the ISCN functionality, submit a ticket through CIBMTR Center Support.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jul 31, 2023

Appendix D: How to Distinguish Infusion Types

This appendix includes definitions of Hematopoietic Cell Transplant (HCT) (including primary and subsequent, autologous cells given for graft failure, and HCT supporting solid organ transplant), Gene Therapies, Cellular Therapies (alone or post-HCT, co-infusion, DLI and micro-transplant). For more information see Table 1.

Table 1.Distinguishing Infusion Types

Infusion	Infusion Type	Purpose of Infusion	Composition of Infusion	Required forms
HCT	HCT, non-genetically modified (Primary or Subsequent)	Replace or repopulate recipient marrow; facilitate hematopoietic recovery; restore donor graft in case of autologous recovery or graft failure.	Must contain HPCs (hematopoietic progenitor cells), also known as CD34+ cells For genetically modified HCTs: CD34+ cells that have been genetically manipulated (modified), but not to treat these types of diseases at the genetic level (i.e. gene therapy).	Pre-TED (2400) Disease Classification (2402)
	HCT, genetically modified (Primary or Subsequent)			
	Autologous Cells Given for Graft Failure (auto rescue)	Restore autologous hematopoiesis; if given after an allogeneic transplant, this often is a temporary measure until next course of action is determined.		
	HCT Supporting Solid Organ transplant	Develop tolerance of solid organ graft via HCT		
Gene Therapy	Gene Therapy	Modified genes to treat or cure disease	Must contain (or does contain?) HPCs (hematopoietic progenitor cells), also known as CD34+ cells.	Pre-TED (2400) Disease Classification (2402)
Cellular Therapy	Cellular Therapy (genetically modified)	The intent is other than to restore hematopoiesis. Examples include but are not limited to: treatment of disease, suboptimal donor chimerism, GVHD prophylaxis/treatment, infection prophylaxis/treatment, immune reconstituion Can be stand-alone or post-HCT	The cells of action are not stem cells, but the infusion may contain residual stem cells (insufficient to cause engraftment). Examples include but are not limited to: lymphocytes, peripheral blood mononuclear cells, dendritic cells from the original donor, and mesenchymal cells. Inlcudes CAR-T, TIL, and TCR products	Pre Cellular Therapy Essential Data (4000)
	Cellular Therapy (non-genetically modified)			
	Donor Lymphocyte Infusion			Donor Lymphocyte Infusion (2199)
	Co-Infusion (with HCT)			Reported with the HCT on Pre-TED (2400)
	Micro-transplants			Pre Cellular Therapy Essential Data (4000)
	Regenerative Medicine	Restoration of organs / tissues excluding blood and marrow	Dependent on which organ/tissue is targeted for restoration	Pre Cellular Therapy Essential Data (4000)

Preparative Regimen
A preparative regimen may or may not be given in all scenarios and is no longer used to define infusion type.

Granulocyte Infusions
Granulocyte infusions given solely to fight infection should not be reported as a HCT or cellular therapy. Contact CIBMTR Center Support for further clarification regarding how to correctly report granulocyte infusions.

HCT Definitions

Hematopoietic Stem Cell Transplant (HCT) – Primary or Subsequent

An HCT, genetically modified or not, is *an infusion of a product (see Appendix E) that contains CD34+ cells.* The intention of a HCT is generally to restore hematopoiesis by replacing or repopulating the recipient marrow. A HCT is often preceded by a preparative regimen, which is used to kill normal cells, malignant cells (if present), and to prevent rejection. However, a preparative regimen may not always be used prior to a stem cell infusion. Examples of this may include a "boost" or infusions given for non-malignant diseases. These indications are still considered a HCT if they fit primary criteria used to define a transplant: the product infused contains CD34+ cells with the intent to restore hematopoiesis.

A **genetically modified** HCT product consists of cells with modified protein expression of stem cells (i.e. not to express CD33), but not modified to treatment of a disease at the genetic level (see gene therapy definition)

Report infusions of bone marrow, cord blood, and mobilized PBSC as a HCT; as a general rule of thumb, infusion of portions of original HCT product without further manipulation would be considered subsequent transplants. The intent of these infusions is generally to restore hematopoiesis.

> ! If the recipient is on a clinical trial and it is felt the above is not the appropriate way to report in accordance with the protocol, please contact CIBMTR Center Support for guidance.

> ! The clinical definition of a subsequent transplant at your center may differ from that of CIBMTR. In order to standardize data, please refer to the above definition for reporting. Phrases such as "stem cell boost" in the medical record should cue the reporting staff to further investigation into what product was infused, and why the product was infused.

HCT Examples Outside of Standard Context

1. Recipient receives an allogeneic related HCT. The product is collected via a standard G-CSF mobilization. A portion of cells from the first HCT are saved for a second infusion. The portion of cells are then manipulated for CD34+ selection and infused. This second infused is considered an HCT because there are sufficient CD34+ cells for engraftment.
2. Recipient receives an allogenic HCT. They never engrafted post-HCT & receive additional HPCs (hematopoietic progenitor cells, CD34+) to restore hematopoiesis. This infusion should be reported as a subsequent HCT because the intent is to restore hematopoiesis.
3. FCRx product is comprised of donor peripheral blood-derived bioengineered hematopoietic stem cells. Mature graft versus host disease (GVHD)-producing and antigen-presenting cells were removed from the donor blood, for induction of immunological tolerance during organ transplantation and enriched for facilitating cells. Kidney transplant patients treated with FCRx were fully withdrawn from immunosuppression without loss of engraftment and achieved durable chimerism. Product contains

high dose of CD34+ cells that could/would lead to engraftment, this in fusion should be reported as an HCT. Source: http://discovery.lifemapsc.com/regenerative-medicine/cell-therapy-applications/blood-fcrx-bioengineered-hematopoietic-stem-cells-for-immunological-tolerance

4. Recipient receives an allogeneic unrelated (MUD) HCT. The PBSC product was collected in a total of 6 bags. Five of these bags were infused as the first HCT. The last bag was infused 6 months later as a "boost". This infusion should be reported as a subsequent HCT because the intent is to restore hematopoiesis.

Autologous Cells Given for Graft Failure

A recipient may receive an infusion of autologous cells as a result of poor hematopoietic recovery or graft failure/rejection following prior allogeneic or autologous transplant; this is generally referred to as "autologous rescue." The CIBMTR defines this type of infusion as a subsequent HCT; however, because the research value of these data does not justify the additional reporting burden to transplant centers, CIBMTR does not currently require additional forms in the event of these transplants. Necessary data are adequately captured on the routine follow-up forms.

HCT Supporting Solid Organ Transplant

immunosuppression, a recipient may receive an infusion of cells prior to a subsequent solid organ transplant. These infusions contain sufficient CD34 cells to result in engraftment and should be reported as an HCT.

Gene Therapy Definition

Genetic diseases are conditions caused by one or more mutations in the genome (chromosomes containing DNA). Gene therapy is a way to treat these types of diseases at the genetic level with an autologous HCT using CD34+ cells that that have been genetically manipulated (modified). The intention of the autologous HCT is to restore hematopoiesis by replacing or repopulating the recipient marrow. The autologous HCT is typically preceded by a preparative regimen.

There are two general approaches to gene therapy: (1) gene addition, where correct copies of genes are inserted into the DNA of the stem cells using a vector system, and (2) gene editing, where defective DNA sequences at a specific location are removed or replaced with the correct sequence.

Genetically Unmanipulated (Unmodified) Autologous Cells Given for Graft Failure

A recipient may receive an infusion of unmanipulated autologous cells ("back-up cells") as a result of poor hematopoietic recovery following a prior autologous transplant with a genetically manipulated product. The CIBMTR defines this type of infusion as a subsequent autologous HCT because there are sufficient CD34+ cells for engraftment; however, because the research value of these data does not justify the additional reporting burden to transplant centers, the data for the infusion is reported on the standard Gene Therapy Product Infusion form.

Cellular Therapy Definitions

Cellular Therapy (Alone or Post-HCT)

Cellular therapy is a form of immunotherapy that is commonly used to treat recurrent disease infections (e.g. viral), or mixed chimerism. Treatment strategies include isolation and transfer of specific stem cell populations, administration of effector cells (e.g. cytotoxic T-cells), induction of mature cells to become pluripotent cells, and reprogramming of mature cells (e.g. CAR T-cells).

The infused product does not contain sufficient CD34+ cells to result in engraftment and the intent is not to restore hematopoiesis. The recipient does not routinely receive a preparative regimen prior to receiving a cellular therapy; however, chemotherapy or immunotherapy that is not sufficient to ablate the marrow to the point where stem cell support is required may be given prior to a cellular therapy.

A cellular therapy should not be reported if additional donor cells (containing CD34+ cells) are given for failed ANC recovery, partial or poor ANC recovery, loss of graft, or late graft failure. Hematopoietic progenitor cell products infused for these indications would be considered a subsequent HCT.

A **genetically modified** cellular therapy product consists of cells that were genetically modified outside the body after pheresis (i.e. product collection). The most common example of a genetically modified product is a CAR-T cell. The patient's own cells are modified in a laboratory after collection to recognize a specific target.

A **non-genetically modified** cellular therapy consists of cells that are collected and infused into the patient without any processing, or the product can undergo a cell selection process to restrict the cells to a specific population of cells. The cells are selected but un-modified in any way. Examples of this are (but not limited to) mesenchymal cells, virus specific T cells (VSTS), donor lymphocyte infusions (DLI).

The types of cells used for a cellular therapies include, but are not limited to the following:

- **Lymphocytes:** A therapeutic product from any source containing a fixed or prescribed dose of T-cells
- **Peripheral blood mononuclear cells:** Whole blood collected as a source of nucleated cells (not hematopoietic progenitor cells) intended for therapeutic use other than restoring hematopoiesis
- **Dendritic cells from the original donor**: A therapeutic cell product containing dendritic cells for therapeutic use
- **Mesenchymal cells:** A therapeutic product containing mesenchymal stromal cells for therapeutic use

> ✱ **CAR-T cells**
> CAR-T are manufactured from lymphocytes

Cellular therapy may be given as a stand alone therapy (with no history of HCT) or given post-HCT.

Examples of Cellular Therapy Alone

1. Autologous CAR-T cells to treat hematologic disease. Report the primary indication as cellular therapy on the Indication for CRID Assignment form.
2. Cell therapy for treatment of autism. Report the primary indication as cellular therapy on the Indication for CRID Assignment form.

Examples of Post-HCT Cellular Therapy (e.g., CAR-T, DCI)

1. Recipient receives autologous-derived marrow-infiltrating lymphocytes (MILs) after an autologous HCT for multiple myeloma. The protocol randomizes the infusion of this product to be post-HCT or at relapse. This infusion should be reported as a post-HCT cellular therapy.
2. Recipient receives an autologous HCT and as part of the protocol will also receive a planned NK cell infusion from the same donor on Day 10. This infusion should be reported as a post-HCT cellular therapy.

Co-Infusion (with HCT)

A co-infusion (or supplemental infusion) is defined as an infusion of cells given prior to clinical Day 0 (after the start of the prep regimen) of an HCT or on Day 0 for any reason other than to produce engraftment. An infusion of supplemental cells may be given in conjunction with a preparative regimen for an HCT. A co-infusion is distinct form of cellular therapy as it is given in conjunction with an HCT, either prior to or on the day of HCT.

Examples of supplemental infusions include, but are not limited to the following:

- NK Cells
- T-Regulatory cells (TREG)
- Mesenchymal cells

Co-infusion cells should be reported in the “Donor Information” section of the Pre-TED, in the “Other” and “Specify cell source” fields. The cell source that is intended to produce engraftment should also be reported in the “Donor Information” section of the Pre-TED. When reporting co-infusions, the Cellular Therapy Product form (4003) and Cellular Therapy Infusion form (4006) are required for all recipients. The HCT Infusion form (2006) will capture information regarding the product intended for engraftment.

Co-Infusion Reporting Scenario
A recipient is scheduled to receive an allogeneic HCT infusion along with infusions of alpha / beta depleted T cells.

<u>Three infusions</u>

1. CD34+ HPCs and alpha / beta depleted T cells on 3/1/2016
2. HPCs (pure product) 3/2/2016
3. Modified T cells 3/23/2016

<u>How to report</u>

1. The infusion of CD34+ HPCs on 3/1/2016 is the event date of HCT
2. The infusion of T cells also on 3/1/2016 would be reported as a co-infusion on the pre-TED
3. The T cells infused on 3/23/2016 would be reported as a post-HCT cellular therapy on the appropriate HCT follow up form

Micro-transplant

An example of a micro-transplant is provided below. For further assistance identifying and reporting micro-transplants, contact CIBMTR Center Support.

Micro-transplant Example

A recipient receives an HLA-mismatched related donor micro-transplant as treatment to maintain remission for AML. Donor GCSF-mobilized donor peripheral stem cells (GPBSCs) are infused at a target dose of 1.0 ×108 CD3+ cells / kg (recipient weight). Since the target dose is of CD3+ cells, the dose of CD34+ is insufficient for engraftment. This is reported as a cellular therapy.

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. In addition to documenting the changes within each manual section, the most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

Date	Manual Section	Add/ Remove/ Modify	Description
7/26/ 2024	Appendix D: How to Distinguish Infusion Types	Modify	Version 4 of Appendix D: How to Distinguish Infusion Types of the Forms Instructions Manual released.

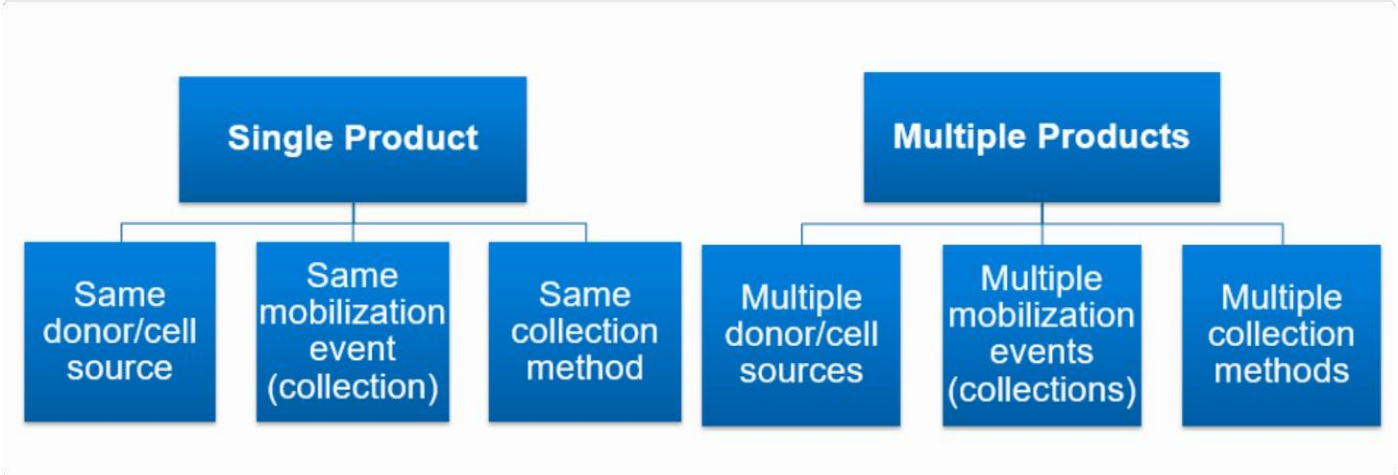
Last modified: Jul 29, 2024

Appendix E: Definition of a Product

The intention of this appendix is to define the term **product** and provide several examples of infusions using single and multiple products. This appendix will also provide direction with regard to reporting product infusion on the CIBMTR Infusion Form 2006.

The Infusion Form 2006 must be submitted for each product. In order for a Form 2006 to become due in the FormsNet3^{SM} application, each product must be reported as a separate instance (including any supplemental cells given prior to clinical day 0) on the Pre-TED Form 2400. If the patient received multiple products of the same type (e.g. multiple PBSC products), the transplant center must contact CIBMTR Center Support to request an additional Form 2006 in FormsNet3^{SM}. Additionally, whenever multiple products are reported on the Comprehensive Report Forms, the transplant center must also contact CIBMTR Center Support to request additional Form 2006s in FormsNet3^{SM}.

Single Product vs. Multiple Products



Single Product: For the purposes of this manual, the CIBMTR defines a single product (i.e. stem cell product) as **cells collected from a single donor using the same mobilization cycle and collection method regardless of the number of collection days.**

If a *single* product is infused, then complete a single (i.e. one) Form 2006. For more information, see Example 1 and Table 1 below.

Example 1 – Multiple Bags: A GCSF-stimulated donor had two PBSC collections on subsequent days. The products collected over the two days were divided into four bags. Although the product is contained in multiple bags, this collection is considered a single product, as there was no change in mobilization technique or collection method. Therefore, one Form 2006 should be submitted.

Example 2 – Change in Mobilization: A GCSF-stimulated donor had a PBSC collection, but the cell count was poor. Plerixafor (Mozobil) was added as part of the mobilization and the donor was recollected

the following day. As the change in mobilization occurred during the same mobilization cycle, these collections are considered a single product. Therefore, a single Form 2006 should be completed.

Multiple Products: For the purposes of this manual, the CIBMTR defines multiple products as cells collected using more than one donor, mobilization technique, and/or collection method.

If a *multiple* products are infused, then multiple (i.e. two or more) Form 2006s must be completed. For more information, see Examples 2-5 and Table 1 below.

Example 3 – Double Cord Blood Units: A recipient receives an infusion of two cord blood units. Two Form 2006s must be submitted as each cord blood unit is from a different donor.

Example 4 – Multiple Collection Methods: A GCSF-stimulated donor had a PBSC collection and the product was cryopreserved. One month later, the donor had a marrow collection and both products were infused at the time of transplant. Each collection is considered a separate product because different collection methods were used. Two Form 2006s must be submitted as these products were collected using two different methods.

Example 5 – Re-Mobilization: A GCSF-stimulated donor had a PBSC collection, but cell count was poor. No further collections were attempted and a week later the donor was re-mobilized with GCSF and a second PBSC collection was performed. Each collection is considered a separate product due to the re-mobilization of the recipient.

Table 1. Single Product vs. Multiple Products

Definition	Number of Form 2006s Required:
Single Product All of the following criteria must be met: • Single donor/cell source • Single mobilization event (collection) • Single collection method	One
Multiple Products One or more of the following criteria must be met: • Multiple donors/cell sources • Multiple mobilization events (collections) • Multiple collection methods	Multiple – one to represent each donor/cell source, mobilization method, and/or collection method

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual

can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for any of the appendices, please reference the retired appendix on the Retired Forms Manuals webpage.

Date	Manual Section	Add/ Remove/ Modify	Description
3/8/21	Appendix E: Definition of a Product	Modify	Graphic below the “Single Product vs Multiple Products” was added and examples 1 – 5 were update.
6/30/17	Appendix E: Definition of a Product	Modify	Appendix P: Definition of a Product has been renamed as Appendix E: Definition of a Product.

Last modified: May 01, 2023

DRAFT Appendix I: Geographic Ancestry

Geographic Ancestry Overview

Ethnicity, Race, and Ancestry Forms Updates
With the Summer 2025 Quarterly Release, ethnicity and race data fields were updated to geographic ancestry. On the Pre-TED (2400) and Cellular Therapy Essential Data Pre-Infusion (4000) forms, the *Ethnicity* and *Race* data fields are disabled. The geographic ancestry and details are only collected on the CIBMTR Research ID Assignment (2804) form. Review below for additional details.

An individual's ancestral background, determined by where generations of their ancestors came from, shapes their genetic composition. How an individual identifies their race, ethnicity, and ancestry helps to understand their genetic composition and is used in transplant clinical research and operations. Collecting more detailed race, ethnicity, and ancestry data provides better access to transplants and cellular therapies, helps to identify the need for more refined patient populations, and supports future research.

The US Office of Management and Budget (OMB) revised *Statistical Policy Directive No.15: Standard of Maintaining, Collecting, and Presenting Federal Data on Race and Ethnicity*. OMB is taking this action to meet its responsibilities to update standards that enhance the ability to compare data across federal agencies and to understand how well federal programs serve a diverse America.

With the Summer 2025 Quarterly Release, CIBMTR approved an expanded race, ethnicity, and ancestry list to meet the OMB Statistical Policy Directive No. 15 requirements, harmonize with NMDP donor ancestry data, and better align with clinical and operational needs of the transplant cellular therapy community.

Geographic Ancestry and Details

Asian
Includes persons with ancestors in any of the original peoples of the Far East, the Indian subcontinent including Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, Philippine Islands, Thailand, Vietnam, Hmong, East India, Laos, Bangladesh, Indonesia, Sri Lanka, Nepal, Bhutan, Sikh, Burma and other South and Southeast Asian.

- **Caribbean Indian**: Includes persons who origins are of the Caribbean and trace their ancestry to Indian subcontinent.

- **Chinese**: Includes persons who origins are of China, or who identified themselves as Cantonese, Tibetan, or Chinese American. In standard census reports, persons who reported as Formosan are included here with Chinese.
- **Filipino**: Includes Filipino, Pilipino, or Philippine.
- **Indian**: Includes persons who origins are of India, including East India, Sikh or who identified themselves as Asian Indian, Bharat, Dravidian, Goan.
- **Japanese**: Includes people whose origins are of Japan, or who identified themselves Nipponese or Japanese American.
- **Korean**: Includes people whose origins are of Korea, or who identified themselves as Korean American.
- **Malaysian**: Includes people whose origins are of Malaysia.
- **Mongolian**: Includes people whose origins are of Mongolia.
- **Pakistani**: Includes people whose origins are of Pakistan.
- **Taiwanese**: Includes people whose origins are of Taiwan.
- **Thai**: Includes people whose origins are of Thailand.
- **Vietnamese**: Includes people whose origins are of Vietname, or who identified themselves as Vietnamese American.
- **Other Indian Subcontinent**: Includes people whose origins are from Bangladesh, Nepal, Sri Lanka, Bhutan.
- **Other Southeast Asian**: Includes people whose origins are from one of the Southeast Asian countries or groups not listed above, including Laos, Hmong, Laohmong, Mong, Cambodia, Indonesia, Singapore Siamese.
- Other Asian – Includes persons from or considering themselves to be Burmese.
- **Not otherwise specific Asian**

Black or African

Includes persons having origins in any of the Black racial groups of Africa, including Black Americans, Africans, Haitians, and residents of Caribbean Islands of African descent.

- **African American**: All persons having origins in any of the Black racial groups of Africa and born or living in the United States.
- **Black Caribbean**: Includes people whose origins are of Haiti or Jamaica.
- **Black South or Central American**: Includes people indicating Black with their origins from South or Central America. Includes countries such as Honduras, Cuba, Nicaragua, Panama, Costa Rica, Chile, Peru, Brazil, Colombia, Venezuela, and Bolivia.
- **East African**: Includes people whose origins are of Ethiopia, Kenya, Somalia, Tanzania.

- **South African**: Includes people whose origins are of Angola, Botswana, Mozambique, Zambia, Zimbabwe.
- **West African**: Includes people whose origins are of Ghana, Mali, Nigeria, Senegal, Liberia.
- **Not otherwise specific Black / African**:

Hispanic or Latino
Refers to people whose ancestors or descendants originated in Central and South America and in the Caribbean.

The phrase Hispanic or Latino excludes people born in Europe whose language is Spanish or Portuguese, and non-Spanish speaking people born in Brazil, Belize, French Guyana, Guyana, Surinam and other non-Spanish speaking territories.

- **Brazilian**: Includes people whose origins are of Brazil.
- **Caribbean Hispanic**: Includes people whose origins are of the Dominican Republic, Guatemala, El Salvador.
- **Cuban**: Includes people whose origins are of Cuba.
- **Mexican**: Includes all citizens of Mexico regardless of ~~race~~ and those born in the United States with Mexican ancestry.
- **Puerto Rican**: Includes all persons of Puerto Rican descent.
- **South / Central American Hispanic**: Includes people whose origins are of countries such as Honduras, Nicaragua, Panama, Costa Rica, Chile, Peru, Colombia, Venezuela, and Bolivia.
- **Not otherwise specified Hispanic / Latino**:

Indigenous American
Includes people having origins in any of the original peoples of the Caribbean, North, South or Central America, and Alaska.

- **Alaska Native**: Includes persons who originated from Alaska, including Inupiat, Yupik, Aleut, Alutiiq, and Egegik.
- **Indigenous Caribbean**: Includes persons who trace their descent from the original people of the Caribbean, such as Arawaks, Caribs (Kalinago), Taíno.
- **Indigenous North American**: Includes persons who trace their descent from any of the original people of North American such as American Indian, Canadian Indian, French-American Indian or Spanish-American Indian.
- **Indigenous South / Central American**: Includes persons who trace their descent from any of the original people of South or Central America such as Mayans or Incas.

- **Not otherwise specified Indigenous American**:

Jewish
An ethno-religious group who has a shared history, culture, and religion, originating from the ancient Middle East.

- **Ashkenazi**: Jewish descent of France, Germany, and Eastern European.
- **Mizrahi**: Jewish descent of the Middle East, North Africa, and Central Asia.
- **Sephardi**: Jewish descent of Spain and Portugal.
- **Not otherwise specified Jewish**:

Middle Eastern or North African
Includes people whose ancestors originated in the Middle East or North Africa.

- **Arab Peninsula**: Includes people whose origins are of United Arab Emirates, Kuwait, Saudia Arabia, Yemen.
- **Central Asian**: Includes people whose origins are of Afghanistan, Iran, Kazakhstan, Turkey.
- **East Mediterranean**: Includes people whose origins are of Iraq, Jordan, Lebanon, Syria.
- **North African**: Includes people whose origins are of Algeria, Egypt, and Morocco,
- **Not otherwise specific Middle Eastern / North African**:

Pacific Islander
Pacific Islander refers to persons having origins in any of the peoples of the Pacific Islands, Guam, Samoa, and Hawaiian Islands.

This category also includes the following groups: Carolinian, Chamorro, Fijian, Guamanian, Kosraean, Marshallese, New Guinean, Northern Mariana Islander, Palauan, Papua, Ponapean (Pohnpelan), Samoan, Solomon Islander, Tahitian, Tarawa Islander, Tokelauan, Tongan, Trukese (Chuukese) and Other Pacific Islanders.

This category does not include individuals who consider themselves “native” to the state of Hawaii simply by virtue of being born there.

- **Melanesian**: Fijian, Papua New Guinean, Solomon Islands,
- **Micronesian**: Includes people whose origins are of the indigenous people of the, Marshall Islands (Marshallese), Caroline Islands (Carolinian), Kosrae (Kosraean), Republic of Palau (Paluan), Pohnpei (Ponapean or Pohneplean), Tarawa Island,

Chuuk, and Mariana Islands (Chamorro), including Guam and Northern Mariana Island.

- **Native Hawaiian**: Includes persons who identify their origins from the Hawaiian Islands chain in the Pacific Ocean.
- **Polynesian**: Includes people whose origins are of the indigenous people of New Zealand (Māori), the Samoan Islands, Tonga, Tahiti, and Tokelau.
- **Not otherwise specific Pacific Islander**: The geographic ancestry is Pacific Islander, but the geographic ancestry details are unknown or does not fit one of the options listed. Includes people who identify their origins as being from any other island in the Pacific Ocean.

White

Includes persons who indicate their race as White such as Canadian, German, Italian, Lebanese, Near Easterner, Arabian, Eastern European, etc.

- **Eastern European**: Includes people whose origins are of countries such as Bulgaria, Georgia, Poland, Romania, Ukraine, Czech Republic, Slovakia, Poland, Croatia, Hungary, and Slovenia.
- **Northern European**: Includes people whose origins are of countries such as Finland, Norway, Sweden, Belgium, Denmark, Austria, Switzerland, Scandinavia.
- **Russian or Former Soviet Union**: Includes people whose origins are of Russia and the Former Soviet Union.
- **Southern European**: Includes people whose origins are of countries such as Greece, Italy, Portugal, Spain.
- **Western European**: Includes persons who identify their origins from countries such as Britian, France, Germany, Ireland, Scottland.
- **White Caribbean**: Includes persons who ancestors came from Europe to Puerto Rico, Cuba or consider themselves Chicano.
- **White South or Central American**: Includes persons who ancestors came from Europe to South Central American countries such as Argentina, Brazil and Mexico.
- Middle East or Near East – A region of southwest Asia, between the India subcontinent and Europe, includes, Israel, Iran, lands west of Pakistan and the other countries of the Arabian Peninsula.
- North Coast of Africa– Includes the northern countries of Africa such as, Sudan, Libya, and Tunisia.
- **Not otherwise specific White**:

Not otherwise specified

Prefer not to answer

Appendix J: Reporting Comorbidities

CIBMTR collects comorbidities data based on criteria from the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI), which was developed and validated by investigators at the Fred Hutchinson Cancer Research Center in Seattle, Washington. The HCT-CI was developed to identify comorbidities relevant to transplant and act as a tool for risk assessment before allogeneic hematopoietic stem cell transplantation. While the criteria were originally developed for use in the adult, allogeneic population, there is utility in collecting these data for all transplant populations, and used in conjunction with other relevant risk factors, these data are useful in determining risk for transplant for the purposes of predicting expected outcomes.

Pediatric Recipients (HCT and CT)
The comorbidity criterion has been updated to include criteria for both adult and pediatric recipients. When discrepancies are identified, seek physician clarification or submit a ticket to CIBMTR Center Support.

What to Report

Report a comorbidity in all the following areas if any of the specified criteria are met.

Comorbidity	Adult Definition and/or criteria	Pediatric Definition and/or criteria	Where to look within the EMR[1]
Arrhythmia	Any history of (but not limited to) one or more of the following which required antiarrhythmic treatment: • Bradycardia (< 50 bpm and sustained) • Tachycardia (> 120 bpm and sustained) • Atrial fibrillation • Sick sinus syndrome • Ventricular arrhythmias	Same as **Adult**	• EKG • Medical administration record • History and physical • Progress notes
Cardiac (Cardiovascular disease)	The presence of one or more of the following: • Any history of coronary artery disease (one or more vessels requiring medical treatment, stent, or bypass) • Any history of myocardial infarction • Any history of congestive heart	Same as **Adult**	• Echocardiogram • Medical administration record • Past surgeries / procedures • History and physical • Progress notes

	failure (regardless of an LVEF >50% at the start of preparative regimen) • LVEF ≤ 50% (or a shortening fraction (SF) of < 26% for pediatric cases) on most recent evaluation prior to the start of the preparative regimen / lymphodepleting therapy		
Cerebrovascular disease	Any history of one or more of the following: • Transient ischemic attack • Cerebrovascular accident/stroke • Subarachnoid, subdural, epidural, or intraparenchymal hemorrhage	Same as **Adult**	• History and physical • Progress notes
Diabetes	Current (within 4 weeks prior to HCT / CT) history of diabetes or steroid-induced hyperglycemia requiring insulin or oral hypoglycemics, not controlled by diet alone.	Same as **Adult**	• History and physical • Progress notes • Medical administration record
Heart valve disease	The presence of one or more of the following, found on the most recent heart evaluation by an echocardiogram: • At least a moderate or severe degree of valve stenosis, regurgitation or insufficiency as determined by echo, whether the valve is mitral, aortic, tricuspid or pulmonary • Prosthetic mitral or aortic valve • Symptomatic mitral valve prolapse	Same as **Adult**	• Echocardiogram • History and physical • Progress notes
Hepatic, mild	Any one or more of the following: • Chronic hepatitis • Any diagnosed history of Hepatitis B or Hepatitis C • Bilirubin > ULN to 1.5 x ULN* • AST or ALT > ULN to 2.5 x ULN*	Same as **Adult**	• Liver function tests (hepatic panel) • History and physical • Progress notes • Infectious disease markers

Hepatic, moderate/ severe	Any one or more of the following: • Liver cirrhosis • Bilirubin > 1.5 x ULN* • AST or ALT > 2.5 x ULN*	Same as **Adult**	• Liver function tests (hepatic panel) • History and physical • Progress notes
Infection	The presence of one or more of the following requiring therapeutic antimicrobial / antifungal / antiviral treatment starting prior to the preparative regimen / lymphodepleting therapy (or prior to Day 0 if no preparative regimen / lymphodepleting therapy is being given) with a recommendation to continue treatment after Day 0: • Documented infection • Fever of unknown origin • Pulmonary nodules suspicious for fungal pneumonia • A positive PPD test requiring prophylaxis against TB • Infection requiring antimicrobial treatment continued after Day 0 *Do not report an infection comorbidity if the infection resolved prior to infusion and there was a recommendation to continue, or the recipient continued medication post-infusion as prophylaxis*	The presence of one or more of the following: • History of invasive fungal infection (refer to *Is there a history of invasive fungal infection?* manual instructions located under the 2400 Comorbid Conditions section for further clarification) • Infection requiring antimicrobial treatment continued after Day 0 *Do not report an infection comorbidity if the infection resolved prior to infusion and there was a recommendation to continue, or the recipient continued medication post-infusion as*	• Infection tests • Purified protein derivative (PPD) test • Radiologic scans • History and physical • Progress notes • Medical administration record

		prophylaxis	
Inflammatory bowel disease	Any history of: • Crohn's disease or • Ulcerative colitis requiring treatment	Same as **Adult**	• History and physical • Progress notes • Medical administration record
Obesity	Body mass index (BMI) > 35.00 kg/m2 • Evaluation of the obesity comorbidity is based on the most recent measurement of the BMI (or weight and height needed for the calculation of BMI) prior to the start of the preparative regimen / lymphodepleting therapy (or prior to Day 0 if preparative regimen / lymphodepleting therapy was not given).	BMI-for-age ≥ 95% during the pre-infusion work-up period. If only the BMI is known, refer to the following link to determine the BMI-for-age: https://www.cdc.gov/growthcharts/. • Evaluation of the obesity comorbidity is based on the most recent measurement of the BMI (or weight and height needed for the calculation of BMI) prior to the start of the preparative regimen / lymphodepleting therapy (or prior to Day 0 if preparative regimen / lymphodepleting therapy was not given).	• History and physical • Progress notes • Weight and / or BMI flow sheet
Peptic ulcer	Any history of peptic ulcer (gastric or duodenal) confirmed by endoscopy or radiologic diagnosis and the recipient has	Same as **Adult**	• History and physical • Progress notes

	or is receiving treatment.		• Endoscopy results • Radiologic scans • Medical administration record
Psychiatric disturbance	Any psychiatric illness requiring treatment, including regular counselling / therapy sessions, within four weeks prior to the pre-infusion work-up period. Treatment also includes the recommendation / prescription of medication and / or regular counselling / therapy sessions but the recipient is non-compliant. Examples of psychiatric disturbances include, but are not limited to, depression, anxiety, Attention-Deficit Disorder (ADD), Attention-Deficit Hyperactivity Disorder (ADHD), schizophrenia, or bipolar disorder. Do not report for recipients only receiving treatment (including counselling / therapy sessions) “as needed” or PRN	Same as **Adult**	• Medical administration record • History and physical • Progress notes
Pulmonary, moderate	Any one or more of the following at the time of pre-infusion evaluation: • Adjusted DLCO 66-80% • FEV1 66-80%** • Dyspnea on slight activity attributed to pulmonary disease and not anemia	Same as **Adult**	• History and physical • Progress notes • Pulmonary function tests
Pulmonary, severe	Any one or more of the following at the time of pre-infusion evaluation: • Adjusted DLCO ≤ 65% • FEV1 ≤ 65%** • Dyspnea at rest attributed to pulmonary disease and not anemia • Requires intermittent or continuous supplemental oxygen	Any one or more of the following at the time of pre-infusion evaluation: • Adjusted DLCO ≤ 65% • FEV1 ≤ 65%** • Dyspnea at rest attributed to pulmonary disease and not anemia	• History and physical • Progress notes • Pulmonary function tests

		• Requires intermediate or continuous supplemental oxygen • History of mechanical ventilation (refer to *Is there a history of mechanical ventilation (excluding COVID-19 (SARS-CoV-2)?* manual instructions located under the 2400 Comorbid Conditions section for further clarification) ◦ Do not report if intubated due to premature birth for <24 hours.	
Renal, moderate/ severe	Any one or more of the following: • Serum creatinine > 2 mg/dL or 177 µmol/L • On dialysis in pre-infusion evaluation period • Prior renal transplant recipient	Any one or more of the following: • Serum creatinine > 2 mg/dL or 177 µmol/L • eGFR <60 ml>2 (by Bedside Schwartz calculation for <18 years old,	• History and physical • Progress notes • Serum creatinine tests

		CKD-EPI calculation for ≥18 years old) • On dialysis in pre-infusion evaluation period • Prior renal transplant recipient	
Rheumatologic	Any history of rheumatologic disease requiring treatment including: • Systemic lupus erythematosus • Rheumatoid arthritis • Sjogren' • Polymyositis • Dermatomyositis • Mixed connective tissue disease • Polymyalgia rheumatic • Polychondritis • Psoriatic arthritis • Sarcoidosis • Vasculitis syndromes	Same as **Adult**	• Medical administration record • History and physical • Progress notes
Prior malignancy	Any solid tumor(s),hematologic malignancy(ies), and / or skin malignancy(ies) that have been treated at any time point in the recipient's past history. Treatment includes surgery and/ or resection. A history of any benign tumor(s) should not be reported. If the recipient is receiving an infusion for a disease that transformed from one disease to another (i.e., MDS to AML, CLL to NHL), the original malignancy should not be reported as a comorbidity. Details regarding disease transformation will be captured on the Pre-TED Disease Classification (2402) Form. For more information regarding disease combinations and transformations, refer to the Common Disease Combinations and Common Disease Transformations tables in the Primary Disease for HCT	Same as **Adult**	• Medical administration record • Past surgeries / procedures • History and physical • Progress notes

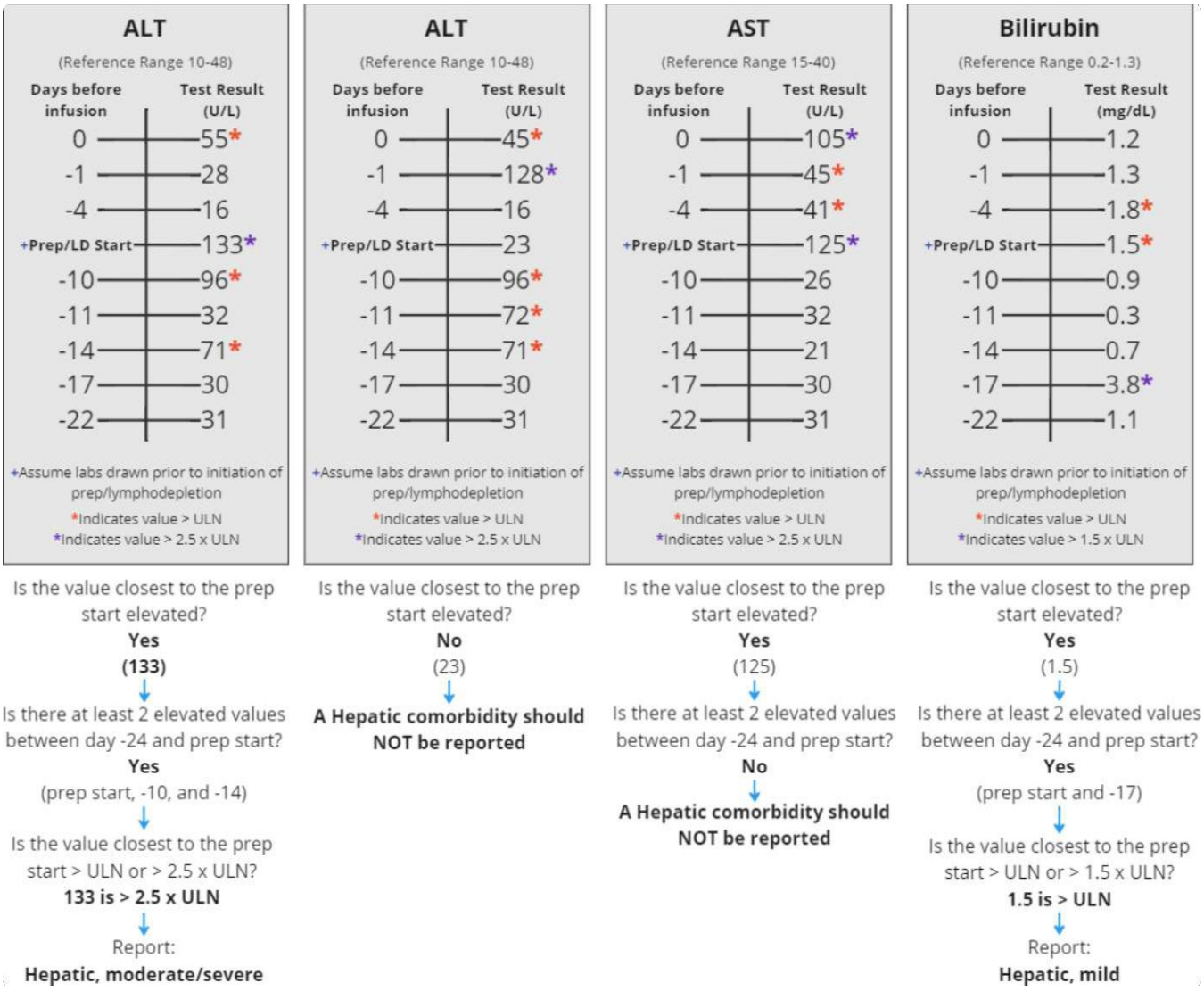
	section of the Pre-TED Disease Classification (2402) Form.		

[1] Examples of where to find source documents within the EMR; however, this will vary from institution to institution. Seek physician clarification on where to find this information, as needed.
(*) ULN refers to upper limit of normal for respective laboratory study
(**) If the PFT lists both a “control” FEV1 and “post-dilator” FEV1, the “control” FEV1 should be used to determine if a pulmonary comorbidity is present.

Prior Skin Malignancies
All prior skin malignancies that have been treated should be reported as a **Prior malignancy** comorbidity; however, only melanoma will be given an HCT-CI score. If an **Other skin malignancy (basal cell, squamous)** is selected, an HCT-CI score is not given.

Hepatic and Renal Comorbidities
In addition to the guidelines listed, include the following time-specific guidelines when reporting hepatic and renal comorbidities
Hepatic Comorbidity: The assessment of liver function tests (ALT, AST and/or Total Bilirubin) has to include at least two values per test (i.e., ALT, AST, or total bilirubin) on two different days (these values do *not* have to be consecutive values) within a period extending between day -24 and the start of the preparative regimen. If only a single value is available in this time period, use values available between days -40 & -25 as the second value. In addition, if the liver function test values closest to the start of the preparative regimen are within normal limits, a hepatic comorbidity should not be reported. *When determining the severity of the hepatic comorbidity, the value closest to the start of the preparative regimen / lymphodepleting therapy should be used.*
Renal (Moderate/Severe) Comorbidity: Serum creatinine > 2 mg/dL or > 177 µmol/L, as detected in at least two lab values on two different days (these values do *not* have to be consecutive values) within a period extending between day -24 and the start of the preparative regimen. If only a single value is available in this time period, use values available between days -40 & -25 as the second value. If the serum creatinine value closest to the start of the preparative regimen is within normal limits, a renal (moderate/severe) comorbidity should not be reported.

[2] Sorror, M. L. (2013). How I assess comorbidities before hematopoietic cell transplantation. *Blood*, 121(15), 2854-2863.



Determine relevant comorbidities through careful review of the recipient medical record. Reviewed documentation should include the recipient's past medical history and objective data from the pre-infusion work-up, including pulmonary function tests, echocardiogram, body weight, and laboratory results. The recipient medication list should be correlated with the past medical history to verify there are not any medications that do not align with the recipient's medical history; if there were to be medications commonly used for a certain purpose not listed in the medical history, further clarify if a relevant comorbidity is present. However, if the medical record remains ambiguous, after careful review, as to whether a condition meets the criteria for reporting comorbidity, do not report.

Report all comorbidities meeting criteria at time of pre-infusion evaluation. This may include comorbidities secondary to the primary infusion disease or conditions resulting from prior therapy and persisting or meeting criteria for reporting at the time of infusion.

For instances in which the pulmonary function testing report does not correct diffusing capacity of carbon monoxide for hemoglobin, use the Dinakara equation to correct.

To correct an uncorrected DLCO:
*corrected DLCO= uncorrected DLCO/(0.06965*hemoglobin)*
where hemoglobin is measured in g/dL

What not to report

The following conditions are not relevant transplant outcomes or risk, and should not be reported under the comorbidities section.

- Acne
- Behavioral issues
- Benign tumor (removed)
- Bulging discs
- Cataracts
- Concussions
- Congenital alopecia
- Deafness or hearing loss
- Fibromyalgia
- Fractures
- Gallbladder (stones, sludge)
- Gastric bypass surgery
- Gastritis
- GERD
- Gestational diabetes (resolved)
- Glaucoma
- Glomerulosclerosis (assume Cr okay)
- Glucose-6-phosphate dehydrogen
- Glucose intolerance
- Gout
- Headaches (chronic)
- Hemorrhoidectomy
- Hemorrhoids
- Hernia
- Hypercholesterolemia
- Hyper-eosinophilia (if not disease related)
- Hyperlipidemia
- Hyperparathyroidism
- Hypertension
- Hypertriglyceridemia
- Hysterectomy
- Iron deposition or overload
- Irritable bowel syndrome (IBS)
- Kidney stones
- Knee arthritis
- Knee surgery
- Lyme disease
- Macular degeneration
- Malabsorption
- Malnutrition
- Meniere's disease
- Menorrhagia
- Microalbuminuria
- Migraines
- Multiple Sclerosis
- Non-alcoholic steatohepatitis (NASH)
- Prior h/o necrotizing fasciitis
- Neonatal jaundice
- Nephritis
- Nephrolithiasis
- Neuropathy
- Neurosyphilis
- Neutropenic colitis
- Obesity with BMI ≤ 35.00 kg/m^2
- Osteoarthritis
- Osteomyelitis
- Osteopenia
- Osteoporosis
- Pancreatitis
- Paraplegic
- Paresthesias
- Parkinson's Disease
- Restless leg syndrome
- Rosacea
- Scoliosis
- Seizure disorders
- Shingles
- Sleep apnea
- Solitary kidney
- Spastic colon
- Splenectomy
- Subdural hematoma
- Syncope
- Thalassemia (minor or trait)
- Thyroidectomy
- Thyroid nodules
- Tonsillectomy
- Tracheoesophageal fistula
- Transient arrhythmia, untreated
- Traumatic brain injury (TBI)
- Tremors
- Tubal ligation
- Uterine fibroids
- Valve insufficiency (mild)
- Valve prolapse (asymptomatic)
- Valve regurgitation (mild)
- Vasculitis
- Vasectomy
- Vena cava filter

• Insomnia • Iron deficiency anemia	• Psoriasis • Raynaud's Disease	• Vertigo • Vision (blindness, blurred) • Vitamin deficiency (B12, D) • Vitiligo • Whipple procedure • Wisdom tooth extraction

Manual Updates:

Sections of the Forms Instruction Manual are frequently updated. In addition to documenting the changes within each manual section, the most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

Date	Manual Section	Add/ Remove/ Modify	Description
7/26/ 2024	Appendix J: Reporting Comorbidities	Modify	Reformatted comorbidity criteria by separating adult criteria from pediatric
12/ 20/ 2023	Appendix J: Reporting Comorbidities	Add	Prior Skin Malignancy blue box added: ***Prior Skin Malignancies****: All prior skin malignancies that have been treated should be reported as a* ***Prior malignancy*** *comorbidity; however, only melanoma will be given an HCT-CI score. If an* ***Other skin malignancy (basal cell, squamous)*** *is selected, an HCT-CI score is not given.*
12/ 20/ 2023	Appendix J: Reporting Comorbidities	Add	Clarification added for mild hepatic criteria: *Hepatic, mild: Any one or more of the following:* • *Chronic hepatitis* • *Any diagnosed history of Hepatitis B or Hepatitis C*
10/5/ 2023	Appendix J: Reporting Comorbidities	Add	Further clarification added for pediatric invasive fungal infections: ***Infection: Pediatrics****: The presence of one or more of the following:* *- History of invasive fungal infection (refer to Is there a history of invasive fungal infection? manual instructions located under the 2400 Comorbid Conditions section for further clarification)* *- Infection requiring antimicrobial treatment continued after Day 0* *Do not report an infection comorbidity if the infection resolved prior to infusion and there was a recommendation to continue, or the recipient continued medication post-infusion as prophylaxis*
10/5/ 2023	Appendix J: Reporting	Add	Further clarification added for pediatric mechanical ventilation: ***Pulmonary, severe****:* ***Pediatrics****: Any one or more of the following at the time of pre-*

	Comorbidities		*infusion evaluation:* *- Adjusted DLCO ≤ 65%* *- FEV1 ≤ 65%*** *- Dyspnea at rest attributed to pulmonary disease and not anemia* *- Requires intermediate or continuous supplemental oxygen* *- History of mechanical ventilation (refer to Is there a history of mechanical ventilation? manual instructions located under the 2400 Comorbid Conditions section for further clarification)* *Do not report if intubated due to premature birth for <24 hours.*
8/28/2023	Appendix J: Reporting Comorbidities	Add	Version 4 of Appendix J added. This version is an overhaul of the appendix for easier comorbidity reporting

Last modified: Jul 29, 2024

Appendix L: Karnofsky / Lansky Performance Status

Karnofsky/Lansky Performance Status

The CIBMTR uses Karnofsky / Lansky performance status to determine the functional status of a recipient. Recipient performance status is a critical data field that has been determined to be essential for all outcome-based analyses. The Karnofsky Scale is designed for recipients aged 16 years and older, and the Lansky Scale is designed for recipients one year old to less than 16 years old. Use this scale (see table 1) to determine the score (10 – 100) that best represents the recipient's activity status at the requested time point.

If a Karnofsky / Lansky score is not documented in the source documentation (e.g., inpatient progress note, physician's clinic notes), data management professionals should not assign a performance score based on analysis of available documents. Rather, a physician or mid-level health care provider (NPs and PAs) should provide documentation of the performance score. Documentation from an RN who has been trained and authorized to determine performance scores may also be used.

Table 1. Karnofsky/Lansky Scale

Karnofsky Scale (recipient age ≥ 16 years)	**Lansky Scale (recipient age ≥ 1 year and <16 years)**
Able to carry on normal activity; no special care is needed	**Able to carry on normal activity; no special care is needed**
100 Normal, no complaints, no evidence of disease	**100** Fully active
90 Able to carry on normal activity	**90** Minor restriction in physically strenuous play
80 Normal activity with effort	**80** Restricted in strenuous play, tires more easily, otherwise active
Unable to work, able to live at home, cares for most personal needs, a varying amount of assistance is needed	**Mild to moderate restriction**
70 Cares for self, unable to carry on normal activity or to do active work	**70** Both greater restrictions of, and less time spent in active play
60 Requires occasional assistance but is able to care for most needs	**60** Ambulatory up to 50% of time, limited active play with assistance/supervision
50 Requires considerable assistance and frequent medical care	**50** Considerable assistance required for any active play, fully able to engage in quiet play
Unable to care for self, requires equivalent of institutional	**Moderate to severe restriction**

or hospital care, disease may be progressing rapidly	
40 Disabled, requires special care and assistance	**40** Able to initiate quite activities
30 Severely disabled, hospitalization indicated, although death not imminent	**30** Needs considerable assistance for quiet activity
20 Very sick, hospitalization necessary	**20** Limited to very passive activity initiated by others (e.g., TV)
10 Moribund, fatal process progressing rapidly	**10** Completely disabled, not even passive play

Karnofsky/Lansky Performance Score vs. ECOG performance score

The CIBMTR recognizes some centers prefer to collect and use the ECOG performance as opposed to the Karnofsky / Lansky score. Although the ECOG and Karnofsky / Lansky performance score systems are based on similar principles, the scales are not the same. For example, the Karnofsky / Lansky scale is described in 11 categories, whereas the ECOG performance status is reported in six categories. Due to the overlap between the two systems, an ECOG score of “one” can represent either “80” or “90” on the Karnofsky / Lansky scale.

For centers that collect only the ECOG performance score, CIBMTR will make the following accommodations when auditing the source data:

- Centers collecting ECOG scores should do so using standard practices to ensure accuracy.
- For the purposes of CIBMTR reporting, the conversion of ECOG to Karnofsky / Lansky should follow standard and consistent practice. This practice should be clear and reproducible.

To convert the ECOG to Karnofsky / Lansky and for more information regarding the conversion, see the memorandum and worksheet example found in Appendix L of the ‘Appendices’ section of the Retired Forms Manuals webpage.

Manual Updates:
Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

To reference the historical Manual Change History for this form, review the table below or reference the retired manual section on the Retired Forms Manuals webpage.

Date	Manual Section	Add/ Remove/ Modify	Description
1/24/ 2025	Appendix L: Karnofsky / Lansky Performance Status	Modify	Version 2 of Appendix L: Karnofsky / Lansky Performance Status released with the Winter 2025 Quarterly release

Last modified: Jan 27, 2025

Reporting Instruction Overview

This section is intended to provide a summary of instructions for questions asked across multiple forms. As this section evolves, many of the examples and repeat instructions listed in multiple manuals will be moved to this section to provide consistent instructions amongst forms.

Links to Sections:

- Lines of Therapy

Last modified: May 02, 2024

Contact Dates

This section is intended to provide general information about reporting contact dates for infusions (transplant, cellular therapy, and gene therapy).

- Determining Contact Dates
- Subsequent Infusions and Contact Dates

Manual Updates

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for this form, please reference the retired manual section on the Retired Forms Manuals.

Date	Manual Section	Add/ Remove/ Modify	Description
7/26/ 2024	Reporting Instructions Overview: Contact Dates	Add	Contact Dates Reporting Instruction Overview added.
4/19/ 2025	Reporting Instructions Overview: Contact Dates – Subsequent Infusions and Contact Dates	Add	Example 4 added: *The recipient had a subsequent auto transplant for graft failure and death occurred in the same reporting period. The recipient has their first transplant on 3/1/2023 and a subsequent auto transplant for the indication of graft failure/insufficient hematopoietic recovery on 4/15/2023 and death occurred on 5/20/2023. Report the Day 100 contact date as the date of death, 5/20/2023.*
4/19/ 2025	Reporting Instructions Overview: Contact Dates – Subsequent Infusions and Contact Dates	Add	Subsequent Cell Therapy and Death blue box added: ***Subsequent Cell Therapy and Death****: For a subsequent cellular therapy, if the Cellular Therapy Essential Data Pre-Infusion (4000) is requested via CIBMTR Center Support to be made "NRQ", the death and subsequent infusion can be reported on the same form.*
4/19/ 2025	Reporting Instructions Overview: Contact Dates – Subsequent	Add	Example 9 added: *The recipient had a subsequent non-genetically modified cellular therapy and death occurred in the same reporting period. The recipient has their first transplant on 1/21/23 and a non-genetically modified cellular therapy infusion on 2/15/23. Death occurred on 3/1/23. Report the Day 100 contact date as the date of death, 3/1/23*

	Infusions and Contact Dates		

Last modified: Apr 21, 2025

Determining Contact Dates

Contact Dates

Contact dates are dates collected on all post-infusion TED, CRF, and cellular therapy (CTED) forms. Contact dates are important as they determine the reporting window for each reporting period and ensure there are no gaps in time for post-infusion follow-up. The contact date data field cannot be left blank and is required to be reported.

Determining Contact Dates

The contact date should represent a date where there was actual contact with the recipient to determine the medical status for the current reporting period, based on a medical evaluation conducted by a clinician with the responsibility for the recipient's care. Acceptable evaluations include those from the transplant center, referring physician, or other physician currently assuming responsibility for the recipient's care. When possible, report a clinician evaluation that falls within the appropriate range, rather than other types of recipient contact that may be closer to the actual time point. In the absence of contact with a clinician, other contact, such as a documented phone call with the recipient or any other documented recipient interaction, may be used to establish the contact date.

In general, the date of contact should be reported as close to the 100-day, 6 month, or annual anniversary of infusion as possible. If an evaluation was not performed at Day+100, at 6 months, or on the infusion anniversary, choose the date of the visit closest to the actual time point. Time windows are provided below to guide selection of dates for reporting purposes. In scenarios where the recipient was not seen within the time windows used for reporting contact dates, some discretion is required when determining which date to report. If the recipient is not seen within the time window, report the date closest to the date of contact within reason (review example 1 and 2 for more information).

Time Point	Approximate Range
100 Days	+ / – 15 days (Day 85 – 115)
6 Months	+ / – 30 days (Day 150 – 210)
1 Year	+ 60 days (Day 366 – 425)
Annual Reporting 2+ Years	+ / – 30 days (Months 23 – 25, 35 – 37, etc.)

If the recipient is alive but has not been seen by a clinician during the entire reporting period but the survival status is known, complete the Survival Tool referenced in the CIBMTR Data Management Guide.

The following examples assume efforts were undertaken to retrieve outside medical records for the primary care provider, but no documentation was received.

- **Example 1**: *The 100-day date of contact doesn't fall within the ideal approximate range.*

    - The autologous recipient was transplanted on 1/1/2013 and is seen regularly until 3/1/2013. After that, the recipient was referred home and not seen again until 7/1/2013 for a restaging exam and 7/5/2013 for a meeting to discuss the results.
        - Report the Day 100 contact date as 3/1/2013 as there was no contact closer to the ideal date of 4/11/2013 and the six-month contact date as 7/5/2013. The Day 100 form cannot be made lost to follow.
- **Example 2**: *The 100-day date of contact doesn't fall within the ideal approximate range and the recipient wasn't seen again until one-year post-HCT.*
    - The autologous recipient was transplanted on 1/1/12 and is seen regularly until 3/1/2012. After that, the recipient was referred home and not seen again until 1/1/2013 for a restaging exam and 1/4/2013 for a meeting to discuss the results.
        - Report the Day 100 contact date as 3/1/2012 as there was no contact closer to the ideal date of 4/11/2012. Report the six-month form as Lost to Follow-Up in FormNet3^{SM} and report the one-year contact date as 1/4/2013.

Reminders

A date of contact should never be used multiple times for the same recipient's forms.

- **Example 3**: 6/1/2013 should not be reported for both the six-month and one-year forms. Instead, determine the best possible date of contact for each reporting period; if there is not a suitable date of contact for a reporting period, this may indicate that the recipient was lost to follow-up.

If the recipient has a disease evaluation just after the ideal date of contact, capturing that data on the form may be beneficial.

- **Example 4**: if the recipient's 90-day restaging exam was delayed until day 115 and the physician had contact with the recipient on day 117, the restaging exams can be reported as the latest disease assessment and day 117 would be the ideal date of contact, even though it is just slightly after the ideal approximate range for the date of contact.

One Year Contact Date for Post-TED (2450) and Post-Infusion Follow-Up (2100)

> **One Year Contact Date**
> This rule applies to HCT and does not apply to gene therapy infusions.

- **Example 5**: *A recipient is evaluated before and after Day 365*
    - The recipient had an allogeneic transplant on 1/5/2013 and is seen regularly until 6/20/2013. After that, the recipient was referred home and not seen again until 1/1/14 for a restaging exam and again on 1/15/2014 to review the results. Day 365 is 1/5/2014.
        - Report the one-year contact date as 1/15/2014 since this date is > Day 365.
- **Example 6**: *A recipient is evaluated before and after Day 365*
    - The recipient is transplanted on 2/28/2019 and seen regularly until 8/28/2019. The next visit is

on 2/20/2020 for blood work and the lab results are phoned to the recipient on 2/21/2020. The recipient was not evaluated again until 4/1/2020. Day 365 is 2/28/2020.

- Report the one-year contact date as 4/1/2020 since this date is > Day 365.

For more information regarding reporting partial or unknown dates, see General Instructions, General Guidelines for Completing Forms.

Section Updates:

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

Last modified: Jul 29, 2024

Subsequent Infusions and Contact Dates

If the recipient has a subsequent infusion (HCT or cellular therapy), the date of contact will depend on the type of subsequent infusion.

- **Subsequent HCT or genetically modified cellular therapy (i.e., CAR-T)**
  - Report the date of contact as the day before the preparative regimen / systemic therapy begins for the subsequent infusion. If no preparative regimen / lymphodepleting therapy is given, report the date of contact as the day before the subsequent infusion.
  - In these cases, actual contact on that day is **not** required, and the day prior to the initiation of the preparative regimen (or infusion if no preparative regimen / lymphodepleting therapy) should be reported. This allows every day to be covered by a reporting period but prevents overlap between infusion events. This is an exception to the standard date of follow-up reporting to ensure all dates are captured within the sequence of forms.

> ✱ **Subsequent Cellular Therapies**
> For a subsequent cellular therapy, if the Cellular Therapy Essential Data Pre-Infusion (4000) is requested via CIBMTR Center Support to be made “NRQ”, then the date of contact should be appropriate to the reporting period .

- **Subsequent non-genetically modified cellular therapy infusion (i.e., DLI, other DCI)**
  - Report the date of contact as appropriate to the reporting period.

Review the examples below for additional information and examples regarding subsequent infusions:

> ✱ **New Forms Due for Subsequent Infusions**
> For all subsequent infusions (transplant, gene therapy, cellular therapy), a new Pre-TED (2400) and Disease Classification (2402) or Cellular Therapy Essential Data Pre-Infusion (4000) Forms will come due, along with the appropriate post-infusion forms. If the subsequent infusion is a DLI, only the Donor Lymphocyte Infusion (2199) Form will come due.

Transplant and Gene Therapy Scenarios

> ✱ **Subsequent Infusions: Gene Therapy**
> Gene therapy infusions are reported on HCT forms and follow the same rules.

Example 1: *The recipient had a subsequent transplant with a preparative regimen.*

- The recipient has their first transplant on 1/1/2021 and a planned second transplant on 2/1/2021. The recipient was admitted and received their first dose of chemotherapy for the preparative regimen for

HCT #2 on 1/28/2021.
    - Report the Day 100 contact date as the day prior to the preparative regimen, 1/27/2021, regardless of actual contact on that date.

Example 2: *The recipient had a subsequent transplant without a preparative regimen.*

- Following their first transplant on 1/1/2021, a recipient with SCID required a subsequent allogeneic transplant due to poor graft function. The recipient has remained inpatient following the first transplant. The physician planned the second transplant for 5/31/2021 and proceeded without a preparative regimen.
    - Report the Day 100 contact date as 4/11/2021 (this date is + / – 15 days of the Day 100 anniversary date)
    - Report the six-month contact date as the appropriate date for the reporting period, 5/30/2021.

Example 3: *The recipient had a subsequent auto transplant for graft failure.*

- The recipient has their first transplant on 3/1/2023 and a subsequent auto transplant for the indication of graft failure/insufficient hematopoietic recovery on 4/15/2023.
    - Report the Day 100 contact date as the appropriate date for the reporting period since a new Pre-TED (2400) / Disease Classification (2402) is not required for auto rescues.

Example 4: *The recipient had a subsequent auto transplant for graft failure and death occurred in the same reporting period.*

- The recipient had their first transplant on 3/1/2023 and a subsequent auto transplant for graft failure / insufficient hematopoietic recovery on 4/15/2023; however, the recipient passed away on 5/20/2023.
    - Report the Day 100 contact date as the death, 5/20/2023.

Example 5: *The recipient had a subsequent gene therapy with a preparative regimen.*

- The recipient has their first transplant on 10/1/2023 and received a gene therapy infusion on 12/2/2023. The recipient was admitted and received their first dose of chemotherapy for the preparative regimen for the gene therapy on 11/29/203.
    - Report the Day 100 contact date as the day prior to the preparative regimen, 11/28/2023, regardless of actual contact on that date.

Subsequent Cellular Therapies
For a subsequent cellular therapy, if the Cellular Therapy Essential Data Pre-Infusion (4000) is requested via CIBMTR Center Support to be made “NRQ”, then the date of contact should be appropriate to the reporting period

Subsequent Cell Therapy and Death

For a subsequent cellular therapy, if the Cellular Therapy Essential Data Pre-Infusion (4000) is requested via CIBMTR Center Support to be made "NRQ", report the death and subsequent infusion on the same form.

Example 6: *The recipient had a subsequent genetically modified cellular therapy with lymphodepleting therapy administered prior to infusion.*

- The recipient has their first transplant on 3/1/2022 and a genetically modified (e.g. CAR-T) cellular therapy infusion on 4/1/2022. The recipient was admitted and received their first dose of lymphodepleting therapy on 3/28/2022.
    - Report the Day 100 contact date as the day prior to the preparative regimen, 3/27/2022 (regardless of actual contact on that date). Both HCT and CTED forms will be completed simultaneously, but all applicable HCT follow-up forms will be reset to the new event date (i.e., Forms 4100+2450 or Forms 4100+2100). See Combined-Follow Up Scenarios (HCT + CT (Genetically Modified)) in the Data Management Manual for more information on combined follow up.

Example 7: *The recipient had a subsequent genetically modified cellular therapy without lymphodepleting therapy administered prior to infusion.*

- The recipient has their first transplant on 3/1/2022 and a genetically modified (e.g. CAR-T) cellular therapy infusion on 4/1/2022. The recipient was admitted and did not receive lymphodepleting therapy prior to infusion.
    - Report the Day 100 contact date as the day prior to infusion, 3/31/2022 (regardless of actual contact on that date). Both HCT and CTED forms will be completed simultaneously, but all applicable HCT follow-up forms will be reset to the new event date (i.e., Forms 4100+2450 or Forms 4100+2100). See Combined-Follow Up Scenarios (HCT + CT (Genetically Modified)) in the Data Management Manual for more information on combined follow up.

Example 8: *The recipient had a subsequent non-genetically modified cellular therapy.*

- The recipient has their first transplant on 1/21/23 and a non-genetically modified cellular therapy infusion on 2/15/23. Lymphodepleting therapy may or may not be given and does not affect the contact date.
    - Report the Day 100 contact date as a date appropriate to the reporting period. Unlike example 5 and 6, combined follow-up will not be applied. HCT reporting continues uninterrupted.

Example 9: *The recipient had a subsequent non-genetically modified cellular therapy and death occurred in the same reporting period.*

- The recipient had their first transplant on 1/21/2023 and a non-genetically modified cellular therapy infusion on 2/15/2023; however, the recipient passed away on 3/1/2023.
    - Report the Day 100 contact date as the date of death, 3/1/2023.

On Demand DLI Reporting
DLIs can be reported prior to the Post-TED (2450) or Post-Infusion follow up (2100) Form due date by creating a Indication for CIBMTR Data Reporting (2814) Form on demand. When the Post-TED (2450) or Post-Infusion follow up (2100) form is completed at the due date, and no other infusions were given in the reporting period, report the DLI as a subsequent infusion, which will create a new Indication for CIBMTR Data Reporting (2814) Form. Submit a ticket via CIBMTR Center Support to request the form be made NRQ.

Example 10: *The recipient had a subsequent Donor Lymphocyte Infusion (DLI).*

- The recipient has their first transplant on 1/21/22 and receives a DLI on 2/27/2022. Lymphodepleting therapy may or may not be given and does not affect the contact date.
    - Report the Day 100 contact date as a date appropriate to the reporting period. A DLI (2199) form should be completed for each DLI received in the reporting period.
    - The Post-TED (2450) or Post-Infusion follow up (2100) form should not be completed early to report a DLI.

Cellular Therapy Scenarios

New Forms Due for Subsequent Infusions
For all subsequent infusions (transplant, gene therapy, cellular therapy), a new Pre-TED (2400) and Disease Classification (2402) or Cellular Therapy Essential Data Pre-Infusion (4000) Forms will come due, along with the appropriate post-infusion forms. If the subsequent infusion is a DLI, only the Donor Lymphocyte Infusion (2199) Form will come due.

Example 11: *The recipient had a subsequent cellular therapy with lymphodepleting therapy administered prior to infusion.*

- The recipient has their first cellular therapy infusion on 1/21/23 and a subsequent cellular therapy infusion on 2/15/2023. The recipient was admitted and received their first dose of lymphodepleting therapy on 2/12/2023.
    - Report the Day 100 c/ontact date as the day prior to the preparative regimen, 2/11/2023 (regardless of actual contact on that date).

Example 12: *The recipient had a subsequent cellular therapy without lymphodepleting therapy administered prior to infusion.*

- The recipient has their first transplant on 1/21/23 and subsequent cellular therapy infusion on 2/15/23. The recipient was admitted and did not receive lymphodepleting therapy.
    - Report the Day 100 contact date as the day prior to infusion, 2/14/23, regardless of actual contact on that date.

Example 13: *The recipient receives a subsequent HCT with a preparative regimen after a genetically*

modified cellular therapy.

- The recipient had a cellular therapy on 1/1/2020 and was seen regularly through the first 100 days. The recipient was admitted and received their first dose of chemotherapy for the preparative regimen for the HCT on 1/28/2020.
    - Report the Day 100 contact date as the da prior to the preparative regimen, 1/27/2022 (regardless of actual contact on that date). Both HCT and CTED follow up forms will be completed simultaneously, but all applicable cellular therapy follow-up forms will be reset to the new event date (i.e., Forms 2450+4100 or Forms 2100+4100). The forms will then have the same event date and due date. See Combined-Follow Up Scenarios (HCT + CT (Genetically Modified)) in the Data Management Manual for more information on combined follow up.

Example 14: *The recipient receives a subsequent HCT without a preparative regimen after a genetically modified cellular therapy.*

- The recipient had a cellular therapy on 1/1/2020 and was seen regularly through the first 100 days. The recipient was admitted and proceeded without a preparative regimen for the HCT on 1/28/2020.
    - Report the Day 100 contact date as the day prior to infusion, 1/27/2022 (regardless of actual contact on that date). Both HCT and CTED follow up forms will be completed simultaneously, but all applicable cellular therapy follow-up forms will be reset to the new event date (i.e., Forms 2450+4100 or Forms 2100+4100). The forms will then have the same event date and due date. See Combined-Follow Up Scenarios (HCT + CT (Genetically Modified)) in the Data Management Manual for more information on combined follow up.

Example 15: *The recipient receives a subsequent HCT with a preparative regimen after a non-genetically modified cellular therapy.*

- The recipient had a cellular therapy on 1/1/2022 and was seen regularly through the first 100 days. The recipient was admitted and received their first dose of chemotherapy for the preparative regimen for the HCT on 1/28/2022.
    - Report the Day 100 contact date as the day prior to the preparative regimen, 1/27/2022 (regardless of actual contact on that date).

Example 16: *The recipient receives a subsequent HCT without a preparative regimen after a non-genetically modified cellular therapy.*

- The recipient had a cellular therapy on 1/1/18 and was seen regularly through the first 100 days. The physician planned the subsequent transplant for 2/15/2018 and proceeded without a preparative regimen
    - Report the Day 100 contact date as the day prior to infusion, 2/14/2018 (regardless of actual contact on that date). Reporting on the cellular therapy event will end.

Example 17: *The recipient receives a subsequent gene therapy with a preparative regimen after a genetically modified cellular therapy.*

- The recipient had a cellular therapy on 1/1/18 and was seen regularly through the first 100 days. The recipient was admitted and received their first dose of chemotherapy for the preparative regimen for the gene therapy on 1/28/2018.
    - Report the Day 100 contact date as the day prior to the preparative regimen, 1/27/2022 (regardless of actual contact on that date).

Section Updates:

Question Number	Date of Change	Add/ Remove/ Modify	Description	Reasoning (If applicable)
Example 4	4/19/ 2025	Add	Example 4 added: *The recipient had a subsequent auto transplant for graft failure and death occurred in the same reporting period. The recipient has their first transplant on 3/1/ 2023 and a subsequent auto transplant for the indication of graft failure/insufficient hematopoietic recovery on 4/15/2023 and death occurred on 5/20/2023. Report the Day 100 contact date as the date of death, 5/20/2023.*	Added for clarification
Example 5	4/19/ 2025	Add	Subsequent Cell Therapy and Death blue box added: ***Subsequent Cell Therapy and Death****: For a subsequent cellular therapy, if the Cellular Therapy Essential Data Pre-Infusion (4000) is requested via CIBMTR Center Support to be made "NRQ", the death and subsequent infusion can be reported on the same form.*	Added for clarification
Example 9	4/19/ 2025	Add	Example 9 added: *The recipient had a subsequent non-genetically modified cellular therapy and death occurred in the same reporting period. The recipient has their first transplant on 1/21/23 and a non-genetically modified cellular therapy infusion on 2/15/23. Death occurred on 3/1/23. Report the Day 100 contact date as the date of death, 3/1/23*	Added for clarification

Last modified: Apr 21, 2025

GVHD

This section is intended to provide general information about reporting GVHD.

- General Information
- Acute GVHD
- Chronic GVHD
- GVHD Reporting Examples and Scenarios
- GVHD Treatment

Manual Updates

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for this form, please reference the retired manual section on the Retired Forms Manuals.

Date	Manual Section	Add/Remove/ Modify	Description
7/26/ 2024	Reporting Instructions Overview: GVHD	Add	GVHD Reporting Instruction Overview added.

Last modified: Jul 29, 2024

General Information

Graft versus Host Disease (GVHD) is an immunological phenomenon resulting from the reaction of donor immune cells against major or minor histocompatibility antigens of the recipient. GVHD is primarily caused by donor-derived T-cells. Very rarely, GVHD may occur due to autologous reactivity (autologous GVHD), third party transfusions, or with identical twin transplantation. Factors influencing the severity of GVHD are related to three main categories:

1. Donor or graft
2. Recipient
3. Treatment

The most influential donor/graft factor is the degree of genetic disparity between the donor and the recipient (HLA match), but other risk factors include female donor to male recipient, donor parity, older donors, and T-cell dose. The occurrence of acute GVHD becomes a risk factor for the development of chronic GVHD. Recipient age and prior infections are also factors.

Determination of Acute vs Chronic GVHD

In the past, GVHD was classified as acute or chronic based on its onset following transplant, in addition to other clinical and histological (biopsy or post-mortem) features. Today, there has been increased recognition that acute and chronic GVHD are not dependent upon time since HCT, so determination of acute or chronic should rest on clinical and histologic features. **However, organ staging, and overall grade should only be calculated from the clinical picture, not histology.** Acute GVHD usually begins between 10 and 40 days after HCT but can appear earlier or later. The organs most affected by acute GVHD are the skin, gut, and / or liver. Other sites, such as the lung, may be involved.

Reporting Acute and / or Chronic GVHD Developed versus Persisted

The CIBMTR forms capture if acute and / or chronic GVHD developed or persisted into the current reporting period. These questions are intended to capture if there were active symptoms of acute and / or chronic GVHD in the current reporting period. Additionally, these questions are intended to decrease the reporting burden by not requiring diagnostic GVHD information to be re-reported if it has been previous captured on a prior form. If GVHD was active during the reporting period, one of the two questions must be answered as **Yes**, depending on the type of GVHD being reported:

Acute GVHD

- *Did acute GVHD develop since the date of last report?*
- *Did acute GVHD persist since the date of last report?*

Chronic GVHD

- *Did chronic GVHD develop since the date of the report?*

- *Did chronic GVHD persist since the date of last report?*

There will not be a situation where **Yes** is reported for both the 'developed' and 'persisted' questions.

GVHD Diagnosis Date

The Post-TED (2450) and Post-Infusion Follow-Up (2100) forms capture the diagnosis date of acute and chronic GVHD. The clinical diagnosis date of GVHD should be reported, which may not necessarily be the date when symptoms began. If there is a clinical diagnosis of GVHD but the diagnosis date is unclear, obtain documentation from the physician confirming the clinical diagnosis date.

If the physician cannot determine the exact date, use the process for reporting partial or unknown dates. Review the General Instructions, General Guidelines for Completing Forms for more information.

Occurrence of Both Acute and Chronic GVHD

Diagnosis of Both Acute and Chronic GVHD
- If acute GVHD is diagnosed prior to chronic GVHD, report the diagnosis information, maximum severity of any symptoms, and treatment administered up to the date of diagnosis of chronic GVHD in the acute GVHD section of the form. Do not include any signs, symptoms, or treatment occurring on or after the onset of chronic GVHD when completing the acute GVHD section.
- Report any new or persistent acute GVHD symptoms occurring on or after the onset of chronic GVHD only in the chronic GVHD section. If chronic GVHD was diagnosed in a prior reporting period, report No for questions Did acute GVHD develop and Did acute GVHD persist in each subsequent reporting period. See reporting scenarios included in the Did acute GVHD develop question.

When there is a diagnosis of both acute and chronic GVHD, specific reporting rules are provided, designed to reduce the reporting burden. Review the guidance below to determine how to answer the GVHD data fields when there is a diagnosis of acute and chronic GVHD:

- When completing the acute GVHD section, do not include any signs, symptoms, or treatment occurring on or after the onset of chronic GVHD.
- If chronic GVHD was diagnosed in a prior reporting period, acute GVHD should never be reported after the diagnosis of the chronic GVHD (i.e., acute GVHD will never be reported in subsequent reporting periods).
    - If there are any new or persistent acute GVHD symptoms occurring after the onset of chronic GVHD, those symptoms will be reported in the chronic GVHD section of the form.

Section Updates:

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

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Last modified: Jul 29, 2024

Acute GVHD

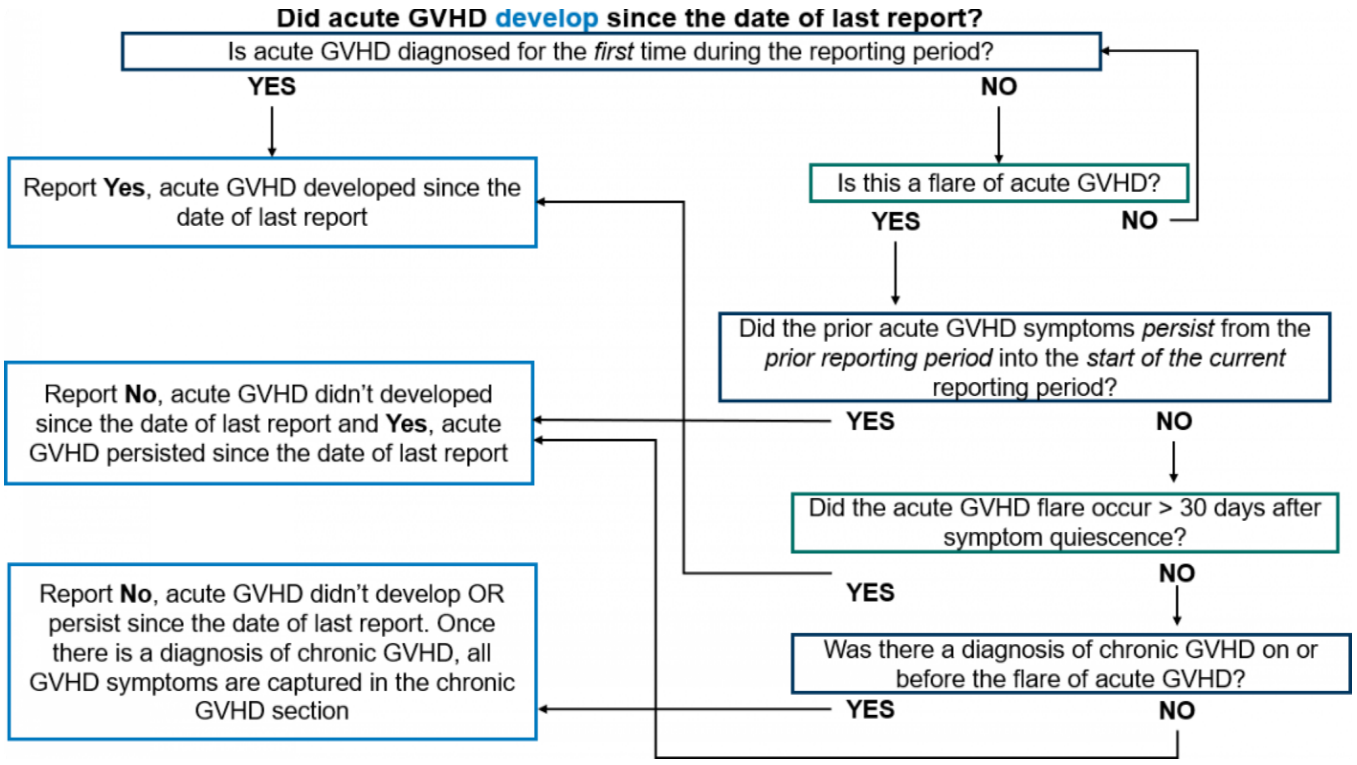
This section provides an overview of reporting acute GVHD data on the Post-TED (2450) and Post-Infusion Follow-Up (2100) Forms.

Development vs Persistence of Acute GVHD

This section is intended to provide guidance on when to report **Yes** or **No** for questions asking if acute GVHD developed or persisted.

> **!** **Transaminitis**
> Previously, if the recipient only had transaminitis related to acute GVHD, acute GVHD would have been reported with the liver stage as 'stage 0' and the overall grade as 'not applicable.' However, as of July 2021, isolated transaminitis should not be reported as acute GVHD. In this scenario, report **No**, acute GVHD did not develop or persist. If the recipient has transaminitis and other organs involved (i.e., skin rash), then report **Yes**, acute GVHD developed or persisted but do not report there was liver involvement.

> ***** **Acute and Chronic GVHD Diagnosis**
> Review the GVHD: General Information for guidance on how to GVHD when acute and chronic GVHD is present.



Did acute GVHD develop since the date of last report should be answered as **Yes** in the following scenarios:

- Acute GVHD was diagnosed for the first time during the reporting period.
- An acute GVHD flare was diagnosed during the current reporting period and all the following conditions are met:
    - The prior acute GVHD symptoms did not persist from the prior reporting period into the beginning of the current reporting period.
    - The flare was diagnosed after at least 30 days without any active acute GVHD symptoms.
    - The recipient was not diagnosed with chronic GVHD on or before the date of the flare (review the Diagnosis of Both Acute and Chronic GVHD note box above).

If there is active acute GVHD during the reporting period, but does not match either of the scenarios above, this question will most likely be reported as **No** and acute GVHD will be reported as 'persistent.'

Did acute GVHD develop since the date of last report should be answered as **No** in the following scenarios:

- There were no active acute GVHD symptoms during the current reporting period.
- Acute GVHD symptoms were present in the reporting period, but they continued from the previous reporting period into the current reporting period.
- All acute GVHD symptoms during the current reporting period occurred after the diagnosis of chronic GVHD (review the Diagnosis of Both Acute and Chronic GVHD note box above).

The **Unknown** option should only be used when there is no information about the recipient's GVHD status for the *entire* reporting period. This option should be used sparingly and only when no judgement can be made about the presence or absence of GVHD in the reporting period.

> **!** **Persistent GVHD and Day 100 Reporting Period**
> Previously, reporting **Yes** for *Did acute GVHD persist since the date of last report* was not an applicable option for the Day 100 reporting period. However, if there was a prior infusion, the recipient developed acute GVHD in the last reporting period of the previous infusion *and* acute GVHD persisted into the Day 100 reporting period of the current infusion, report **Yes**, acute GVHD persisted since the date of last report.

Did acute GVHD persist since the date of last report should be answered as **Yes** in the following scenarios:

- Acute GVHD was diagnosed in a previous reporting period and the acute GVHD symptoms have been active since diagnosis and continue to be active in the current reporting period (i.e., there is no period of symptom resolution or quiescence since diagnosis).
- Acute GVHD symptoms resolved before the first day of the current reporting period, but a flare occurred within 30 days of symptom resolution / quiescence.
    - The recipient was not diagnosed with chronic GVHD on or before the date of the flare (review the GVHD: General Information for guidance on how to GVHD when acute and chronic GVHD is present).

Did acute GVHD persist since the date of last report should be answered as **No** in the following scenarios:

- There were no active acute GVHD symptoms during the current reporting period.
- All acute GVHD symptoms during the current reporting period occurred after the diagnosis of chronic GVHD (review the GVHD: General Information for guidance on how to GVHD when acute and chronic GVHD is present).

The **Unknown** option should only be used when there is no information about the recipient's GVHD status for the *entire* reporting period. This option should be used sparingly and only when no judgement can be made about the presence or absence of GVHD in the reporting period.

Acute GVHD Grading and Staging Criteria

Acute GVHD Staging and Grading Criteria
The CIBMTR will continue to collect overall grade of acute GVHD data based on the Przepiorka et al. criteria. New methods of grading acute GVHD, such as the MAGIC consortium criteria[1], can be used internally at sites; however, all data reported to the CIBMTR should be consistent with the Przepiorka et al. criteria.

[1] Harris AC, Young R, Devine S, et al. International, Multicenter Standardization of Acute Graft-versus-Host Disease Clinical Data Collection: A Report from the Mount Sinai Acute GVHD International Consortium. Biol Blood Marrow Transplant. 2015;22(1):4–10. doi:10.1016/j.bbmt.2015.09.001

When acute GVHD is reported, the organ staging and overall grade, based on the criteria published by Przepiorka et al., *Bone Marrow Transplant* 1995; 15(6):825-8 is reported at two different time points:

- At diagnosis
  - The period between onset of signs / symptoms and the start of GVHD treatment (topical or systemic). If acute GVHD is reported as 'persisted,' the organ staging and grading at diagnosis data fields are disabled.
- Maximum overall stage and grade
  - Intended to capture the maximum organ staging and grading in the current reporting period. The maximum staging does not need to be at the time when the maximum overall grade occurred. Additionally, the maximum organ staging and grading may differ from the stage / grade at diagnosis or may be the same.
  - When reporting the maximum grade, the date of the maximum grade is also reported.
    - Report the first date when the maximum grade occurred.
    - When there are multiple instances when the same maximum grade occurred, report the earliest date.

Maximum Organ Staging
Based on further clarification, the instructions for reporting the maximum organ staging were

updated with the Fall 2023 Quarterly Release. The intent of the maximum organ staging questions is to capture the maximum stage of each organ involved with acute GVHD within the entire reporting period; not specifically at the time of the maximum overall grade, despite what the question text states.

The 'maximum overall stage and grade' is intended to capture the maximum organ staging and grading in the current reporting period. The maximum staging does not need to be at the time when the maximum overall grade occurred. Additionally, the maximum organ staging and grading may differ from the stage / grade at diagnosis or may be the same. These data fields will be answered for every reporting period when acute GVHD is reported.

Acute GVHD Overall Grade

When acute GVHD is reported, either a new development or persistence of GVHD, the overall grade of acute GVHD will be captured. The acute GVHD grading scale is based on *clinical evidence* (clinician observation), not histology. Pathology reports sometimes list a histologic grade of GVHD. Do not report the histologic grade. GVHD scoring and grading is based on clinical severity, not histologic severity. Biopsy of affected organs allows for more precise diagnosis as to the presence or absence of GVHD. However, *overall grading remains clinical* and is based on the criteria published by Przepiorka et al., *Bone Marrow Transplant* 1995; 15(6):825-8 (refer to the Acute GVHD Grading and Staging table below).

If acute GVHD was present, but the grade was not documented and cannot be determined from the grading and staging table, report the overall grade as **Not applicable**. Examples may include:

- Any other organ involvement without skin, liver, or gut symptoms attributable to GVHD.
- Lower GI involvement where the stage cannot be determined in select scenarios. Review the lower GI involvement description below.

Upper GI GVHD
If the recipient only has upper GI GVHD during the reporting period, report this as overall **grade II**. This may differ from prior instructions regarding how to report upper GI GVHD.

Acute GVHD Grading and Staging Table

Stage	Skin	Liver	Gut
1	Rash on <25% of skin[1]	Bilirubin 2-3 mg/dl[2]	Diarrhea > 500 ml/day[3] or persistent nausea[4] *Pediatric*: 280-555 ml/m^2/day or 10-19.9 mL/kg/day
2	Rash on 25-50% of skin	Bilirubin 3-6 mg/dl	Diarrhea >1000 ml/day *Pediatric*: 556-833 ml/m^2/day or 20-30 mL/kg/day
3	Rash on >50% of skin	Bilirubin 6-15 mg/dl	Diarrhea >1500 ml/day

			Pediatric: >833 ml/m^2/day or > 30 mL/kg/day
4	Generalized erythroderma with bullous formation	Bilirubin >15 mg/dl	Severe abdominal pain, with or without ileus, and / or grossly bloody stool
Grade[5]			
I	Stage 1-2	None	None
II	Stage 3	Stage 1	Stage 1
III	—	Stage 2-3	Stages 2-4
IV[6]	Stage 4	Stage 4	—

[1] Use “Rule of Nines” Percent Body Surfaces table below or burn chart to determine extent of rash.

[2] Range given as total bilirubin. Downgrade one stage if an additional cause of elevated bilirubin has been documented.

[3] Volume of diarrhea applies to adults. For pediatric patients, the volume of diarrhea should be based on body surface area. Downgrade one stage if an additional cause of diarrhea has been documented.

[4] Persistent nausea with or without histologic evidence of GVHD in the stomach or duodenum.

[5] Criteria for grading given as minimum degree of organ involvement required to confer that grade.

[6] Grade IV may also include lesser organ involvement with an extreme decrease in performance status

Acute GVHD Organ Staging

In addition to capturing the overall grade, the staging of each organ involved with acute GVHD is also collected.

Skin

The skin stage is based on the percentage of body surface area (BSA) involved with a maculopapular rash, due to acute GVHD. If the skin stage or BSA percentage is not documented within the medical records, the Percent Body Surfaces table (provided below) should be used to determine the BSA percentage involved with the rash. When determining the rash, do not include BSA affected by a rash not related to acute GVHD.

Percent Body Surfaces Table

Body Area	Percent	Total Percentage
Each Arm	9%	18%
Each Leg	18%	36%

Chest & Abdomen	18%	18%
Back	18%	18%
Head	9%	9%
Pubis	1%	1%

Lower GI GVHD and Stool Output Not Documented
If diarrhea is attributed to acute GVHD during the reporting period, but the volume of stool output is not documented, leave the lower GI stage data field blank, override the FormsNet3 error as "not documented," and specify the volume of stool output was not documented. In this case, report **Not applicable** for the overall grade *unless* stage 4 acute skin GVHD, stage 4 acute liver GVHD, or an extreme decrease in performance status or stage 2 or 3 acute liver GVHD was also documented at the time point being reported (*at diagnosis* or *maximum grade during the current reporting period*.

Lower intestinal tract

The lower GI stage is based on the volume of diarrhea attributed to acute GVHD. For adults, mL / day should be used and for pediatrics, use mL / m^2 / day. In addition to reviewing the progress note, the input and output records may be used when determining the volume of diarrhea. Do not include diarrhea not related to acute GVHD.

Upper intestinal tract

The stage of upper intestinal tract is based on the presence of persistent nausea or vomiting, related to acute GVHD. When reporting the stage of upper GI involvement, do not include nausea or vomiting not attributed to acute GVHD.

Liver

The liver staging is based on elevated bilirubin levels, due to acute GVHD. Transaminitis related to GVHD is not included when determining the liver stage. If there is only isolated transaminitis, do not report acute GVHD occurred. If there is transaminitis and other organs involved (i.e., skin rash), report acute GVHD occurred but do not report there was liver involvement. Additionally, do not include elevated bilirubin not due to acute GVHD.

Other sites

If an organ other than skin, upper GI, lower GI, or liver was affected by acute GVHD, the organ will be specified in the 'other site' data field. Do not report liver if there was isolated transaminitis. In addition, do not report symptoms ongoing but not attributed to acute GVHD.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jul 29, 2024

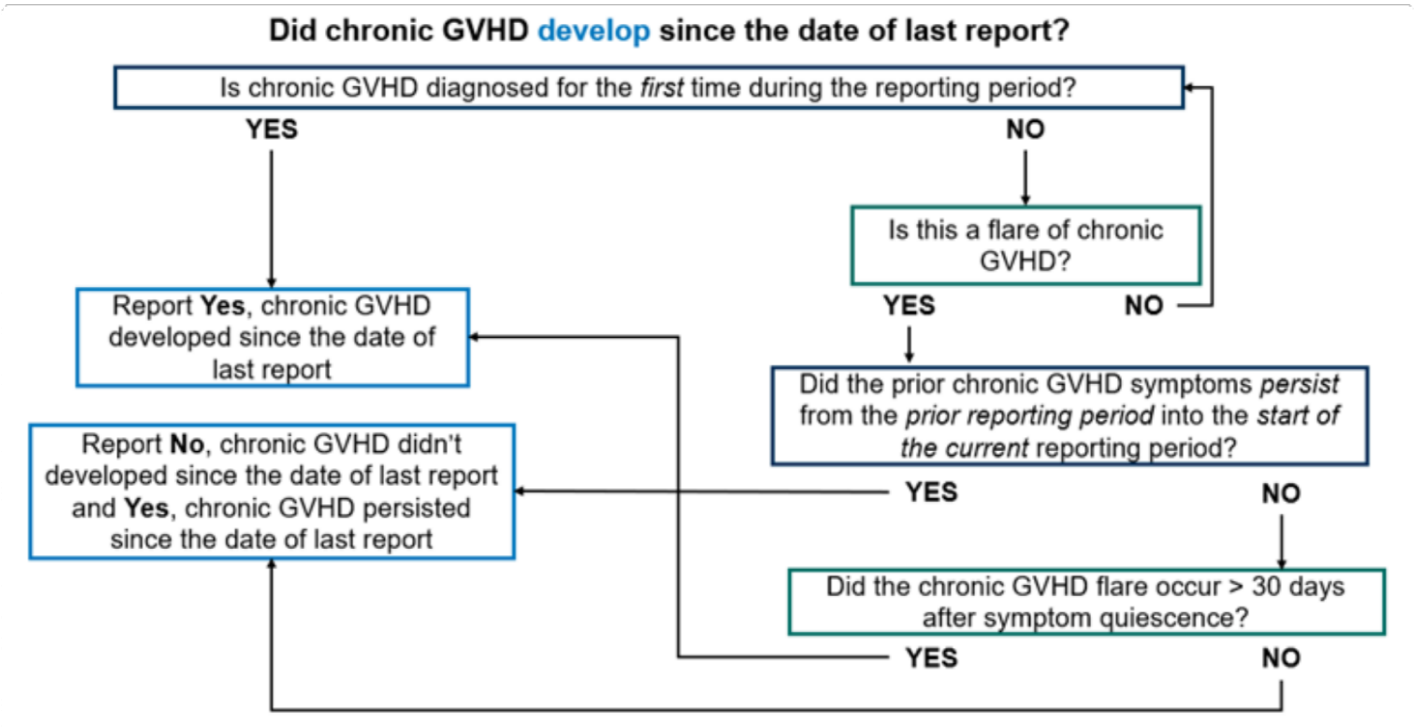
Chronic GVHD

This section provides an overview of reporting chronic GVHD on the Post-TED (2450) and Post-Infusion Follow-Up (2100) Forms.

Development vs Persistence of Chronic GVHD

This section is intended to provide guidance on when to report Yes or No for questions asking if chronic GVHD developed or persisted.

> ✱ **Acute and Chronic GVHD Diagnosis**
> Review the GVHD: General Information for guidance on how to GVHD when acute and chronic GVHD is present.



Did chronic GVHD develop since the date of last report should be answered as **Yes** in the following scenarios:

- Chronic GVHD was diagnosed for the first time during the reporting period.
- A chronic GVHD flare was diagnosed during the current reporting period and all the following conditions are met:
  - The prior chronic GVHD symptoms did not persist from the prior reporting period into the beginning of the current reporting period.
  - The flare was diagnosed after at least 30 days without any active chronic GVHD symptoms.
- Acute GVHD followed by chronic GVHD was previously diagnosed and resolved, a flare of acute

GVHD was diagnosed in the current reporting period, and all the following conditions are met:
    - The prior GVHD symptoms (acute and / or chronic) did not persist from the prior reporting period into the beginning of the current reporting period.
    - The flare was diagnosed after at least 30 days without any active GVHD symptoms (acute and / or chronic).

Did chronic GVHD develop since the date of last report should be answered as **No** in the following scenarios:

- There were no active chronic GVHD symptoms during the current reporting period.
- Chronic GVHD symptoms were present in reporting the period, but they continued from the previous reporting period into the current reporting period.
- Acute GVHD followed by chronic GVHD was diagnosed in a prior reporting period and acute GVHD symptoms persisted into the current reporting period.

The **Unknown** option should only be used when there is no information about the recipient's GVHD status for the entire reporting period. This option should be used sparingly and only when no judgement can be made about the presence or absence of GVHD in the reporting period.

Did chronic GVHD persist since the date of last report should be answered as **Yes** in the following scenarios:

- Chronic GVHD was diagnosed in a previous reporting period and the chronic GVHD symptoms have been active since diagnosis and continue to be active in the current reporting period (i.e., there is no period of symptom resolution or quiescence since diagnosis).
- Chronic GVHD symptoms resolved before the first day of the current reporting period, but a flare occurred within 30 days of symptom resolution / quiescence.
- Acute GVHD followed by chronic GVHD was previously diagnosed and resolved, a flare of acute GVHD was diagnosed in the current reporting period, and one of the following conditions are met:
    - The prior GVHD symptoms (acute and / or chronic) persisted from the prior reporting period into the beginning of the current reporting period.
    - The flare was diagnosed 30 days or less after symptom resolution.

Did chronic GVHD persist since the date of last report should be answered as **No** in the following scenarios:

- There were no active chronic GVHD symptoms during the current reporting period.
- Acute GVHD followed by chronic GVHD was previously diagnosed and resolved, a flare of acute GVHD was diagnosed in the current reporting period, and all the following conditions are met:
    - The prior GVHD symptoms (acute and / or chronic) did not persist from the prior reporting period into the beginning of the current reporting period.
    - The flare was diagnosed after at least 30 days without any active GVHD symptoms (acute and / or chronic).

The **Unknown** option should only be used when there is no information about the recipient's GVHD status for the *entire* reporting period. This option should be used sparingly and only when no judgement can be

made about the presence or absence of GVHD in the reporting period.

Chronic GVHD Grading, Organ Scoring, and Extent Criteria

When chronic is reported, the organ scoring at diagnosis is collected on the Post-Infusion Follow-Up (2100) Form and the maximum overall grade and extent in the reporting period is captured on both the Post-TED (2450) and Post-Infusion Follow-Up (2100) Forms.

Chronic GVHD Maximum Grade

The maximum chronic GVHD involvement, based on the opinion of the clinician (i.e., clinical grade) in the current reporting period is captured. The intent of this question is to capture the maximum grade based on the best clinical judgment. When both the global severity score and the score based on the clinician's opinion is documented, report the clinician score. If the clinician score is not documented, seek physician documentation.

Guidelines on how to report the maximum grade of chronic GVHD are outlined below:

- **Mild**: Signs and symptoms of chronic GVHD do not interfere substantially with function and do not progress once appropriately treated with local therapy or standard systemic therapy (i.e., corticosteroids and / or cyclosporine or tacrolimus).
- **Moderate**: Signs and symptoms of chronic GVHD interfere somewhat with function despite appropriate therapy or are progressive through first line of systemic therapy (i.e., corticosteroids and / or cyclosporine or tacrolimus).
- **Severe**: Signs and symptoms of chronic GVHD limit function substantially despite appropriate therapy or are progressive through second line of therapy.

The **Unknown** option should only be used when there is no information about the recipient's GVHD status for the entire reporting period. This option should be used sparingly and only when no judgment can be made about the status of the recipient's GVHD.

In addition to reporting the maximum grade in the reporting period, the date when the maximum grade occurred is captured:

- Report the first date when the maximum grade occurred.
- When there are multiple instances when the same maximum grade occurred, report the earliest date.

Chronic GVHD Organ Scoring (At Diagnosis)

In addition to capturing the maximum grade, the organ involvement and NIH score of each organ involved at diagnosis of chronic GVHD is also collected. For each organ involvement, specific features present at diagnosis are also reported. Refer to the Organ Scoring of Chronic GVHD Table below for the NIH Consensus Criteria 2014 for organ scoring of chronic GVHD.

Organ Scoring of Chronic GVHD Table

Organ	Score 0	Score 1	Score 2	Score 3
Skin %BSA[1]	No BSA involved	1-18% BSA	19-50% BSA	>50% BSA
Skin Features	No sclerotic features	N/A	Superficial sclerotic features, but not “hidebound”	Deep sclerotic features; “hidebound;” impaired mobility; ulceration
Mouth	No symptoms	Mild symptoms with disease signs but not limiting oral intake significantly	Moderate symptoms with disease signs with partial limitation of oral intake	Severe symptoms with disease signs with major limitation of oral intake
Eyes	No symptoms	Mild dry eye symptoms not affecting ADL (requirement of lubricant drops ≤ 3x/day)	Moderate dry eye symptoms partially affecting ADL (requiring lubricant drops > 3x/day or punctal plugs) WITHOUT new vision impairment due to keratoconjunctivitis sicca (KCS)	Severe dry eye symptoms significantly affecting ADL (special eyewear to relieve pain) OR unable to work because of ocular symptoms OR loss of vision due to keratoconjunctivitis sicca (KCS)
GI Tract	No symptoms	Symptoms without significant weight loss (< 5%)	Symptoms associated with mild to moderate weight loss (5-15%) within 3 months OR moderate diarrhea without significant interference with daily living	Symptoms associated with significant weight loss (> 15%) within 3 months, requires nutritional supplement for most calorie needs OR esophageal dilation OR severe diarrhea with significant interference with daily living.
Liver	Normal total bilirubin and ALT or AP < 3 x ULN	Normal total bilirubin with ALT ≥ 3 to 5 x ULN or AP ≥ 3 ULN	Elevated total bilirubin but ≤ 3 mg / dL or ALT >5 x ULN	Elevated total bilirubin > 3 mg / dL
Lungs Symptom score:	No symptoms	Mild symptoms (SOB after climbing one flight of steps)	Moderate symptoms (SOB after walking on flat ground)	Severe symptoms (SOB at rests; requires O2)
Lungs Lung	FEV1 ≥ 80%	FEV1 60-79%	FEV1 40-59%	FEV1 ≤ 39%

score:				
Joints and Fascia	No symptoms	Mild tightness of arms or legs, normal or mild decreased range of motion AND not affecting ADL	Tightness of arms or legs OR joint contractures, erythema thought to be due to fasciitis, moderate decrease of range of motion AND mild to moderate limitation of ADL	Contractures WITH significant decrease of range of motion *AND* significant limitation of ADL (unable to tie shoes, button shirts, dress self, etc.)
Genital Tract[2]	No signs	Mild signs and females with or without discomfort on exam	Moderate signs and may have signs of discomfort on exam	Severe signs with or without symptoms
Other Features[3]	No GVHD	Mild	Moderate	Severe
NIH Consensus Criteria, 2014 1. Features to be scored by BSA: Maculopapular rash, lichen planus-like features, sclerotic features, papulosquamous lesions or ichthyosis, keratosis pilaris-like GVHD. 2. Scoring is based on severity of the signs instead of symptoms, based on limited available data and the opinions of experts. Female or male genital GVHD is not scored if a practitioner is unable to examine the patient. 3. May include ascites, pericardial effusion, pleural effusion(s), nephrotic syndrome, myasthenia gravis, peripheral neuropathy, polymyositis, weight loss without GI symptoms, eosinophilia > 500/μL, platelets < 100,000/μL, others.				

Skin: Ranges from skin discoloration to severe scarring and tightness. Includes, but not limited to:

- Sclerosis: thickening of the skin, which may cause loss of suppleness
- Maculopapular rash / erythema: reddish skin with small confluent bumps / redness
- Lichen planus-like features: erythematous / violaceous flat-topped papules or plaques with or without surface reticulations or a silvery or shiny appearance.
- Papulosquamous lesions or ichthyosis: dry, scaly, or thickened skin
- Keratosis pilaris: small acne-like bumps and rough patches
- Poikiloderma: atrophy, pigmentary changes, and telangiectasia

In addition to reporting the NIH score BSA involved, the skin features score and the skin GVHD features present at diagnosis is reported. If any skin abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Mouth: Refers to white plaques, scarring, and ulcers occurring in the mouth and throat.

- Lichen planus-like features: whitish lacy patches that usually appear first on inner cheeks, but can

involve roof of mouths, gums, and / or tongue.

If any mouth abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Eyes: Dry eyes and / or corneal ulcers due to keratoconjunctivitis sicca.

- Keratoconjunctivitis sicca (KCS): dry eye syndrome

If any eye abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Gastrointestinal Tract (GI): Includes the following:

- Esophageal web / proximal stricture or ring: extension of esophageal tissue
- Dysphagia: difficulty swallowing
- Anorexia
- Nausea
- Vomiting
- Diarrhea
- Weight loss: weight loss ≥ 5%
- Failure to thrive

If any GI abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Liver: Include all types of liver abnormalities, either clinical or histological. Liver involvement may be manifested by elevation of liver function tests. Three are considered in the scoring system: total bilirubin, alkaline phosphatase; SGPT (ALT).

If any liver abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Lung: Ranges from mild impairment on pulmonary function tests to severe disorder. If a pulmonary function test was completed, the FEV1 percent from the diagnosis of chronic GVHD is reported.

If any lung abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Joints and Fascia: Includes the following:

- Contractures: loss of joint mobility due to skin or fascia changes

If any joint or fascia abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Genital Tract: Includes the following:

- Female: Vaginitis / stricture: pain, ulceration, inflammation, eventually scarring / narrowing of the vaginal opening.
- Male: Pain, burning sensation, lichen planus or lichen sclerosis features, scarring, stenosis.

The recipient's sexually active status will be captured if the genital tract was involved at the diagnosis of chronic GVHD.

If any genital tract abnormalities were present, but explained entirely by non-GVHD causes, the documented causes are specified.

Chronic GVHD Extent

Another grading system for chronic GVHD is divided into two categories, limited and extensive. Definitions of limited and extensive are based on Sullivan KM, Blood 1981; 57:267. The intent of this data field is to capture if chronic GVHD was limited or extensive throughout the entire reporting period and is not dependent on the maximum grade and date of chronic GVHD. If the criteria to report extensive was met at any time in the current reporting period, **Extensive** should be reported. Use the guidelines below to determine how to report the extent.

- **Limited**: Localized skin involvement and / or liver dysfunction attributed to chronic GVHD.
- **Extensive**: Includes any of the following symptoms attributed to chronic GVHD:
    - Generalized skin involvement and / or liver dysfunction.
    - Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis.
    - Involvement of the eye: Schirmer's test with < 5 mm wetting.
    - Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy (labial biopsy not required).
    - Involvement of any other target organ.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jul 29, 2024

GVHD Reporting Examples and Scenarios

Review this section for various GVHD reporting examples.

Example 1: Diagnosis of Acute GVHD with a Flare Over Multiple Reporting Periods

- A recipient receives a HCT on 1/1/2015 and develops acute GVHD which is clinically diagnosed on 2/1/2015. At least one of their symptoms, attributed to acute GVHD, persists beyond the 100-day date of contact which is 4/5/2015. Treatment continues and symptoms completely resolve on 5/1/2015. Immunosuppression is tapered until a flare of acute GVHD is diagnosed on 5/25/2015. Immunosuppression is given and symptoms quickly resolve with no active acute GVHD beginning 6/10/2015. The six-month date of contact is 6/20/2015. Another flare of acute GVHD is clinically diagnosed on 8/15/2015.
    - Day 100: Report **Yes**, acute GVHD developed in the reporting period and the diagnosis date as 2/1/2015.
        - The 'persistence' of acute GVHD question will be disabled.
        - Report the overall grade and organ staging at diagnosis based on the assessments performed at the time of diagnosis (2/1/2015).
    - Six Month: Report **No**, acute GVHD did not develop in the reporting period as the notes indicate the flare of acute GVHD was < 30 days from symptom resolution. This does not count as a new reportable episode.
        - Report **Yes**, acute GVHD persisted into the current reporting period.
        - The overall grade and organ staging at diagnosis data fields will be disabled.
    - One Year: Report **Yes**, acute GVHD developed in the reporting period since the flare of acute GVHD occurred > 30 days after resolving in a prior reporting period and the diagnosis date as the date of the flare (8/15/2015).
        - The 'persistence' of acute GVHD question will be disabled.
        - Report the overall grade and organ staging at diagnosis based on the assessments performed at the time of diagnosis of the acute GVHD flare (8/15/2015).

Example 2: Reporting the Overall Grade with Multiple Organs Involved and Transaminitis

- A recipient developed stage 2 skin involvement and elevated liver function tests (LFTs) attributed to acute GVHD; however, there was no total bilirubin manifestation.
    - Report the overall maximum grade I acute GVHD since the staging / grading can be determined using the GVHD Grading and Staging table above.

Example 3: Isolated Transaminitis

- A recipient developed acute liver GVHD with elevated LFTs (i.e., transaminases) with no total bilirubin manifestation. The progress notes indicate stage 1 (grade II overall) acute GVHD of the liver.
    - Acute GVHD should not be reported as there was only transaminitis.

Example 4: Reporting the Overall Grade with Multiple Organs Involved

- A recipient developed stage 2 skin involvement, which showed improvement in response to topical steroids. However, the recipient then developed hyperbilirubinemia attributed to stage 1 liver involvement; the skin involvement at that time was stage 1.
    - Report grade II as the overall grade (assuming this was the extent of the recipient's acute GVHD in the reporting period).

Example 5: Acute GVHD Followed by Chronic GVHD

- A recipient developed stage 2 skin involvement which resolved in response to topical steroids. Later in the reporting period, the recipient was diagnosed with mild chronic eye GVHD. Shortly thereafter, they were diagnosed with a stage 3 flare of acute skin GVHD.
    - Report the overall acute GVHD grade as grade I. Do not consider any new or persistent acute GVHD symptoms occurring after the onset of chronic GVHD when completing the acute GVHD section of the form.

Example 6: Reporting the Maximum Organ Staging and Overall Grade

- A recipient developed stage 1 skin involvement and stage 1 liver involvement (overall grade II) on 1/1/2019 which resolved in response to topical steroids and tacrolimus. Later in the reporting period, on 2/14/2019, they have a flare of the skin GVHD, this time at stage 3, along with GI stage 1 (overall grade II).
    - Report grade II would be reported as the *maximum overall grade of acute GVHD* with the maximum date reported as 1/1/2019 the *first date of maximum overall grade of acute GVHD*. Additionally, the organ staging should be reported as skin stage 3, liver stage 1, and GI stage 1. The maximum organ staging during the reporting period is captured, not the maximum organ staging at the time of the maximum overall grade.

Example 7: Diagnosis and Resolution of Acute and Chronic GVHD with Acute GVHD Flare

- A recipient receives a HCT on 1/1/2015 and develops acute skin GVHD on 2/1/2015 and then chronic eye GVHD on 3/1/2015. Both acute and chronic symptoms resolved by the 100-day date of contact (4/5/2015). While tapering their immunosuppression, the recipient has a flare of their acute skin GVHD on 5/30/2015. Treatment continues and symptoms completely resolve by the six-month date of contact (6/20/2015).
    - Day 100 Reporting Period
        - Report **Yes**, acute GVHD developed in the reporting period and the diagnosis date as 2/1/2015.
            - The 'persistence' of acute GVHD question will be disabled.
            - Report the overall grade and organ staging at diagnosis based on the assessments performed at the time of diagnosis (2/1/2015).
            - Report the maximum overall grade and organ staging based on any symptoms and treatment documented from the onset of acute GVHD (2/1/2015) until the diagnosis of chronic GVHD (3/1/2015).
        - Report **No**, chronic GVHD did not develop in the reporting period.
    - Six Month Reporting Period

        - Report **No**, acute GVHD did not develop in the reporting period.
        - Report **No**, acute GVHD persisted into the current reporting period.
            - The overall grade and organ staging at diagnosis data fields will be disabled.
        - Report **Yes**, chronic GVHD developed in the reporting period and the diagnosis date as 5/30/2015.

Example 8: Chronic GVHD Organ Scoring

- A recipient developed a maculopapular rash covering 25% BSA as well as deep sclerotic features. Both features are attributed to chronic GVHD.
    - Report **Yes** for skin involvement and specify the score as 3 based on the findings of deep sclerotic features.

Example 9: Scoring Chronic GVHD Involvement with Acute GVHD Symptoms

- A recipient developed a maculopapular rash covering 25% as well as dry eyes. Both findings were identified and diagnosed at the same time. The skin rash was attributed to acute GVHD while the dry eyes were entirely attributed to chronic GVHD.
    - Report **Yes** for skin involvement and score 2 and **Yes** for eye involvement with a score of 1.
        - Any acute findings identified on or after the date of chronic GVHD diagnosis must be reported in the chronic GVHD section. The skin rash is not reported in the acute GVHD section unless it was identified and diagnosed prior to the diagnosis of chronic GVHD.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jul 29, 2024

GVHD Treatment

This section provides an overview of reporting GVHD treatment on the Post-TED (2450) and Post-Infusion Follow-Up (2100) Forms.

Reporting of GVHD treatment is separated into two categories:

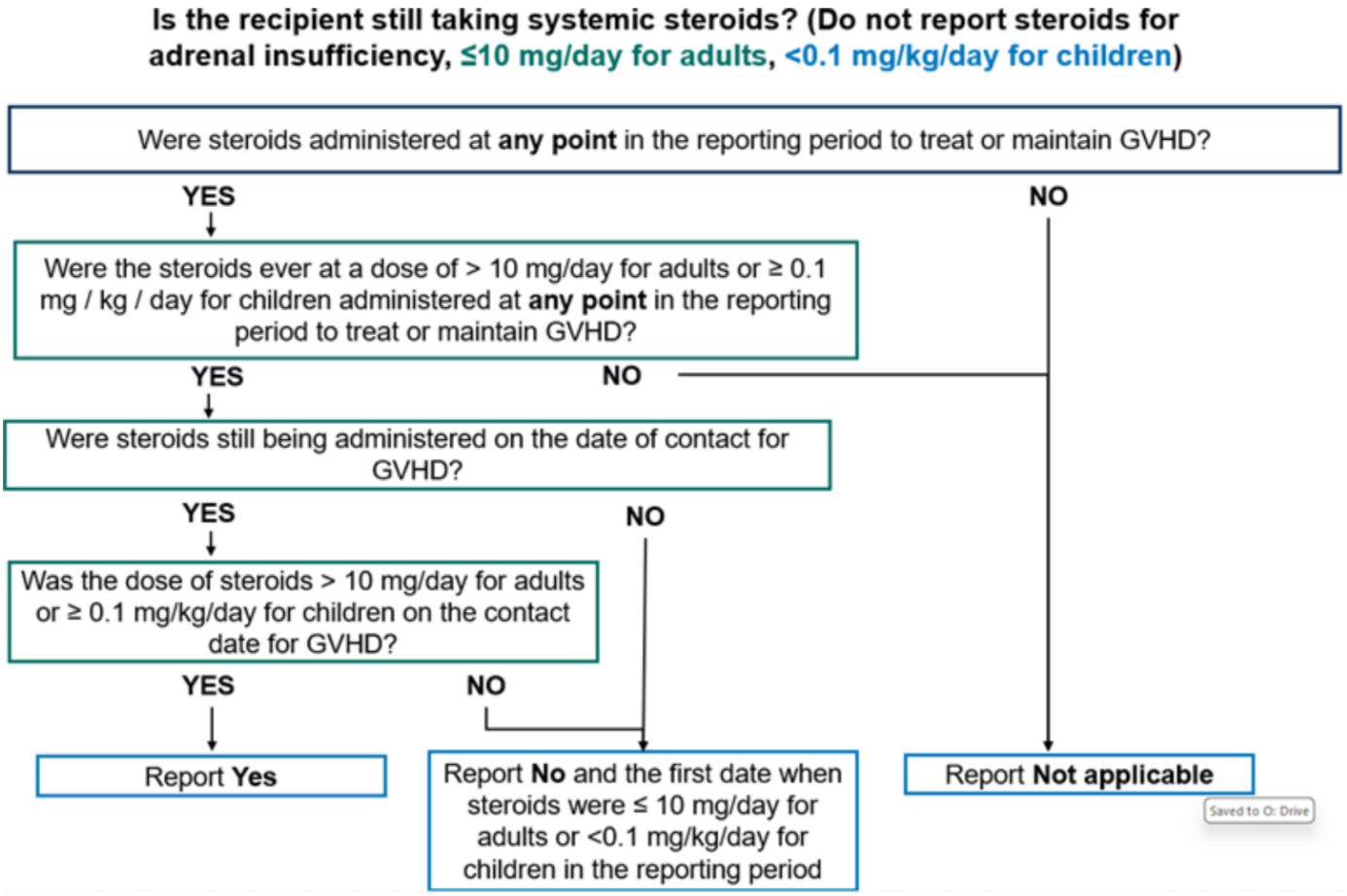
1. Systemic steroids
2. Immunosuppression

Review the information below to determine when to report **Yes**, **No**, **Not applicable**, and **Unknown** for the systemic steroids and immunosuppression GVHD treatment data fields.

Corticosteroids
Corticosteroids are captured differently depending on whether they are used topically or systemically. Use the following guidelines when determining how to report corticosteroids used to treat acute GVHD:
Topical Creams for Skin: Do not report topical ointments or creams used to treat skin GVHD including corticosteroid creams such as Triamcinolone or Hydrocortisone.
Other Topical Treatments: Certain corticosteroid treatments are inhaled or ingested but are not absorbed and are therefore considered topical. Examples include beclomethasone and budesonide. Do not consider these medications when answering *Is the recipient still taking systemic steroids*.
Systemic Treatments: Systemic administration of corticosteroids, including use of prednisone and dexamethasone, should be reported in *Is the recipient still taking systemic steroids*.

Systemic Steroids

The Post-TED (2450) and Post-Infusion Follow-Up (2100) Forms capture if the recipient is still taking systemic steroids on the contact date to treat or prevent GVHD, excluding steroids for adrenal insufficiency. Steroids are considered ‘systemic’ if the dose of steroids are > 10 mg / day for adults and $\underline{\geq}$ 0.1 mg / kg / day for children.



Report **Yes**, the recipient is taking systemic steroids in the following scenarios:

- The recipient is still taking systemic steroids (> 10 mg / day for adults and ≥ 0.1 mg / kg / day for children) to treat or prevent GVHD on the contact date.
- The recipient died prior to discontinuation of systemic steroids used to treat or prevent GVHD.

Report **No**, the recipient is not taking systemic steroids in the following scenarios:

- Systemic steroids (dose > 10 mg / day for adults and ≥ 0.1 mg / kg / day for children) were administered in the current reporting period and discontinued on or before the contact date.
- Systemic steroid (> 10 mg / day for adults and ≥ 0.1 mg / kg / day for children) were administered in the current reporting period and the dose of steroids were decreased to ≤ 10 mg / day for adults or < 0.1 mg / kg / day for children on or before the contact date.

If completing the Post-Infusion Follow-Up (2100) Form and the recipient is no longer taking systemic steroids on the contact date, the date when steroids were discontinued is also captured. This date should be the date when the dose of systemic steroids was decreased to ≤ 10 mg / day for adults or < 0.1 mg / kg / day for children.

For more information regarding reporting partial or unknown dates, see General Instructions, General Guidelines for Completing Forms.

Report **Not applicable** in the following scenarios:

- The recipient has never received systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) to treat or prevent GVHD in the current reporting period.
- This form is being completed for a subsequent HCT and the recipient has never received systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) to treat or prevent GVHD since the start of the preparative regimen for the most recent infusion (or since the date of the most recent infusion if no preparative regimen is given).
- The recipient stopped taking systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) to treat or prevent GVHD in a previous reporting period and did not restart systemic steroids (> 10 mg / day for adults or ≥ 0.1 mg / kg / day for children) during the current reporting period.

The **Unknown** option should be used sparingly and only when there is no information, and no judgement can be made to determine if the recipient is still taking systemic steroids on the contact date.

Systemic Steroids Examples

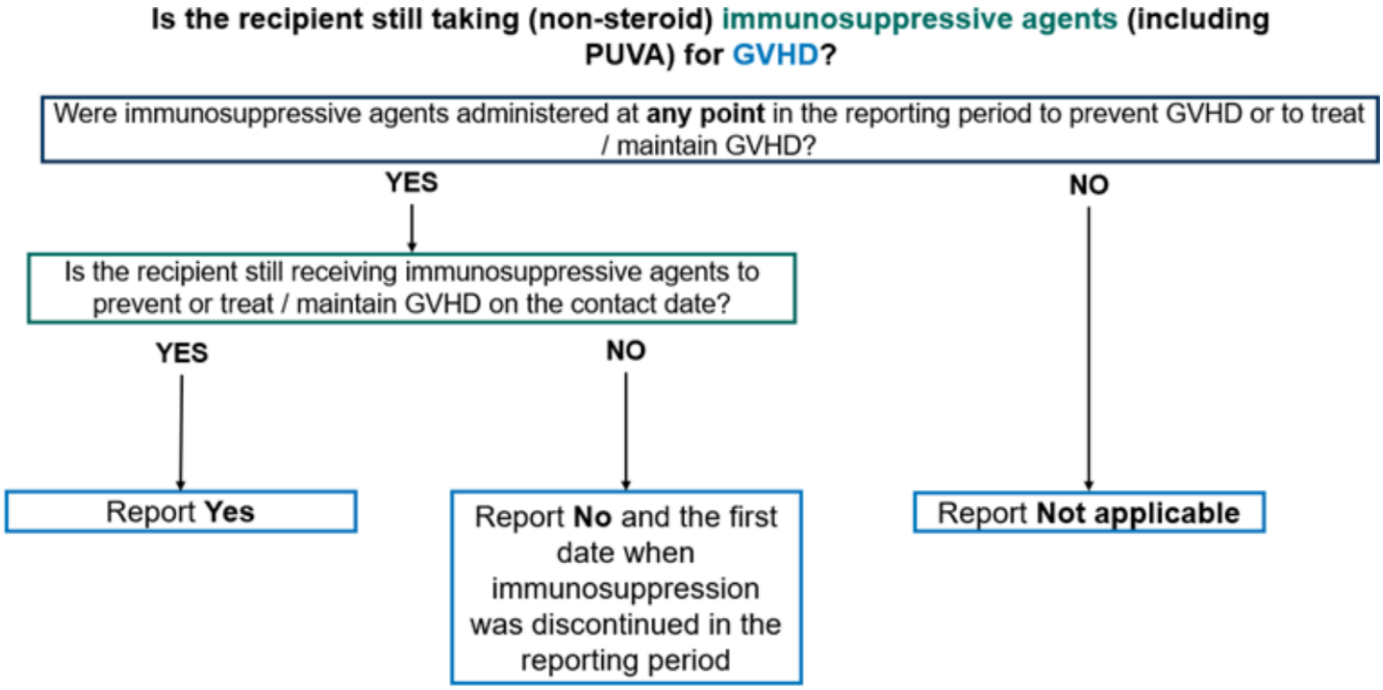
- Example 1: In the Day 100 reporting period, a recipient was started on 60 mg / day of Prednisone to treat GVHD. The recipient's GVHD improved and began weaning the dose of Prednisone. On the Day 100 contact date, the dose of steroids was decreased to 5 mg / day which was continued into the 6-month reporting period, without any dose increases, and eventually discontinued by the end of the 6-month reporting period.
    - Day 100: Report **No**, the recipient is not taking systemic steroids since the dose of steroids is < 10 mg on the contact date.
    - 6-month: Report **Not applicable** since the dose of systemic steroids was never > 10 mg / day during the entire reporting period.
- Example 2: At the beginning of the 6-month reporting period, a recipient is on 20 mg / day of Prednisone. After three months, the dose is decreased to 10 mg per day and is maintained at that level until the end of the reporting period. In this scenario, report **No** since the dose of systemic steroids was ≤ 10 mg / day on the day of contact.
- Example 3: Throughout the Day 100 reporting period, a recipient is on 30 mg / day Methylprednisolone given every other day to treat GVHD. The recipient continues the same dose on the Day 100 contact date. In this scenario the average daily dose is approximately 15 mg / day and therefore, *Is the recipient still taking systemic steroids* should be answered as **Yes**, as the dose of systemic steroids is > 10 mg / day.
- Example 4: At the beginning of the 6-month reporting period, a recipient is only on Budesonide for mild GI GVHD. In this scenario, report **Not applicable** when capturing steroids as Budesonide is considered to be a topical agent and should not be considered when answering *Is the recipient still taking systemic steroids*.
- Example 5: At the beginning of the reporting period, a recipient is started on 40 mg / day Prednisone for acute GVHD on 3/1/2021. After two weeks, the recipient's steroid dose is tapered using the following schedule:
    - 3/14/2021: Prednisone tapered to 30 mg / day
    - 3/20/2021: Prednisone tapered to 20 mg / day
    - 3/25/2021: Prednisone tapered to 10 mg / day

- 3/30/2021: Prednisone tapered to 5 mg/ day

At the end of the reporting period for the question, *Is the recipient still taking systemic steroids* should be answered as **No**. If the recipient is on the CRF reporting track, on the Post-Infusion Follow-up (2100) Form, the date of final steroid administration should be captured as 3/25/2021 as this was the date the recipient's steroid dose fell below the systemic steroid dose threshold of > 10 mg / day.

Immunosuppression

The Post-TED (2450) and Post-Infusion Follow-Up (2100) Forms capture if the recipient is still taking immunosuppression on the contact date to treat or prevent GVHD, excluding steroids for adrenal insufficiency. Immunosuppression includes any non-steroidal immunosuppressive agents, including PUVA. Review the list below or examples of immunosuppressive agents.



Report **Yes**, the recipient is immunosuppression in the following scenarios:

- The recipient is still immunosuppression to treat or prevent GVHD on the contact date.
- The recipient died prior to discontinuation of immunosuppression used to treat or prevent GVHD.

Report **No**, the recipient is not taking immunosuppression in the following scenarios:

- Immunosuppression was administered in the current reporting period and discontinued on or before the contact date.

If completing the Post-Infusion Follow-Up (2100) Form and the recipient is no longer taking immunosuppression on the contact date, the date when immunosuppression was discontinued is also captured. This date should be the date when immunosuppression was discontinued.

For more information regarding reporting partial or unknown dates, see General Instructions, General Guidelines for Completing Forms.

Report **Not applicable** in the following scenarios:

- The recipient has never received non-steroidal immunosuppressive agents (including PUVA) to treat or prevent GVHD.
- This form is being completed for a subsequent HCT and the recipient has never received non-steroidal immunosuppressive agents (including PUVA) to treat or prevent GVHD since the start of the preparative regimen for the most recent infusion (or since the date of the most recent infusion if no preparative regimen was given).
- The recipient stopped taking non-steroidal immunosuppressive agents (including PUVA) to treat or prevent GVHD in a previous reporting period and did not restart non-steroidal immunosuppressive agents (including PUVA) during the current reporting period.

The **Unknown** option should be used sparingly and only when there is no information, and no judgement can be made to determine if the recipient is still taking immunosuppression on the contact date.

Immunosuppressive Agents Examples

- Example 1: Going into transplant, a recipient was taking Tacrolimus and MMF. In the Day 100 reporting period, both drugs were discontinued. In the 6-month reporting period, no new immunosuppressive agents were started.
    - Day 100: Report **No**, for *Is the recipient still taking immunosuppressive agents* as both immunosuppressive drugs were discontinued in the reporting period.
    - 6-month: Report **Not applicable** for *Is the recipient still taking immunosuppressive agents* since the recipient never received immunosuppressive agents within the reporting period.

Immunosuppressive Agents

Below are examples of possible immunosuppressive agents:

- Aldesleukin (Proleukin): Increases production of several white blood cells including regulatory T-cells. This drug is also known as interleukin-2.
- ALG (Anti-Lymphocyte Globulin), ALS (Anti-Lymphocyte Serum), ATG (Anti-Thymocyte Globulin) ATS (Anti-Thymocyte Serum): Serum or gamma globulin preparations containing polyclonal immunoglobulins directed against lymphocytes. These drugs are usually prepared from animals immunized against human lymphocytes.
- Azathioprine (Imuran): Azathioprine inhibits purine synthesis. Usually it is used at low doses in combination with other treatments.
- Bortezomib (Velcade): A proteasome inhibitor.
- Cyclosporine (CSA, Neoral, Sandimmune): Calcineurin inhibitor which decreases cytokine production by T-cells. Usually given for ≥ 3 months.
- Cyclophosphamide (Cytoxan): Given in high doses near the date of infusion as single agent prophylaxis.
- Extra-corporeal photopheresis (ECP): The recipient's blood is removed from the body, exposes to

psoralen and ultraviolet light, and re-infused.

- FK 506 (Tacrolimus, Prograf): Inhibits the production of interleukin-2 by T-cells.
- Hydroxychloroquine (Plaquenil): Hydroxychloroquine inhibits transcription of DNA to RNA and is commonly used as an anti-malarial drug.
- Interleukin Inhibitor: Interleukin inhibitors suppress production of white blood cells and are grouped according to their target. Examples of IL-2 inhibitors include daclizumab (Zynbryta) and basiliximab (Simulect). Examples of IL-6 inhibitors include tocilizumab (Actemra) and siltuximab (Sylvant).
- In vivo monoclonal antibody: Antibody preparations that are infused in the recipient following HSCT.
- In vivo immunotoxin: Antibody preparations linked to a toxin that is infused in the recipient following HCT.
- Janus Kinase 2 Inhibitors: Suppress function of T-effector cells. Examples: ruxoloitinib (Jakafi, Jakavi) and tofacitinib (Xeljanz, Jakvinus).
- Methotrexate (MTX) (Amethopterin): Inhibits the metabolism of folic acid. It is most often used with cyclosporine and is usually for a short duration of time.
- Mycophenolate mofetil (MMF) (CellCept, Myfortic): Inhibits the de novo pathway used for lymphocyte proliferation and activation.
- Pentostatin (Nipent): Inhibits adenosine deaminase, which blocks DNA (and some RNA) synthesis.
- Sirolimus (Rapamycin, Rapamune): Inhibits the response to interleukin-2, blocking the activation of T-cells.
- Tyrosine Kinase Inhibitor (TKI): Suppress function of tyrosine kinases thereby downregulating the function of many other cellular proteins / processes including fibrosis and inflammation. Examples: imatinib (Gleevec, Glivec), nilotinib (Tasigna), and dasatinib (Sprycel).
- UV Therapy: UVA or UVB radiation administered to affected areas of the skin in order to suppress proliferation of cells responsible for GVHD.
    - PUVA (Psoralen and UVA): Psoralen is applied or taken orally to sensitize the skin, and then the skin is exposed to UVA radiation.
    - UVB: Broadband- or Narrowband-UVB radiation is applied to the affected areas of the skin.

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Jul 29, 2024

Lines of Therapy

This section is intended to provide general information about reporting pre-infusion lines of therapy, along with disease-specific lines of therapy information. The disease-specific lines of therapy information will be posted over time.

- General Reporting
- Lines of Therapy: Acute Lymphoblastic Leukemia
- Lines of Therapy: Plasma Cell Disorders

Manual Updates

Sections of the Forms Instruction Manual are frequently updated. The most recent updates to the manual can be found below. For additional information, select the manual section and review the updated text.

If you need to reference the historical Manual Change History for this form, please reference the retired manual section on the Retired Forms Manuals.

Date	Manual Section	Add/Remove/ Modify	Description
4/19/ 2024	Reporting Instructions Overview: Lines of Therapy	Add	Lines of Therapy Reporting Instruction Overview added.

Last modified: Apr 21, 2024

General Reporting

Pre-infusion lines of therapy data fields capture data related to drugs, surgery, and radiation therapy used to treat the primary disease for infusion. Additionally, the best response to the line of therapy, and relapse / progression following therapy is captured.

This section provides general instructions used for all diseases when reporting the pre-infusion lines of therapy on the disease specific forms.

Reporting Lines of Therapy

A single line of therapy refers to any agent administered during the same time period with the same intent (i.e., induction, consolidation, etc.).

In general, when the disease status changes resulting in a change of treatment, a new line of therapy should be reported. When there is a change in therapy because a favorable response was not achieved, a new line of therapy should be reported.
For many diseases, but not all, when there is a change in therapy (i.e., swapping of drugs, discontinuation of drugs, dose change), due to a toxicity, all drugs can be reported as a single instance. Review the disease-specific lines of therapy sections for information on reporting separate lines of therapy, depending on the disease, if applicable.

- PCD Lines of Therapy

For information on how to report COG therapies for recipients with ALL, review the ALL Lines of Therapy section.

First vs Subsequent Infusions: Which Therapy to Report

All therapy since the initial diagnosis should be reported on the pre-infusion disease-specific forms. Review the guidelines below to determine which therapies to report when there was a prior infusion (HCT or CT).

- If there was a prior infusion and a pre-infusion disease specific form was not previously completed, report all lines of therapy administered from the time of the original diagnosis up to the infusion that is being reported.
- If there was a prior infusion and a pre-infusion disease specific form was previously completed, report lines of therapy administered following the prior infusion up until the infusion that is being reported.

Intent of Therapy

Depending on the diseases-specific pre-infusion form, the intent of therapy is captured. Below is common terminology used for describing the intent of therapy.

- Induction: The first line of therapy following diagnosis to achieve complete remission.

- Re-induction: Therapy given if the first line of therapy fails to produce a complete remission or relapse occurs.
    - The disease-specific forms do not have a re-induction option.
        - Report this type of therapy as **Induction** if the first line of therapy did not produce complete remission.
        - Report this type of therapy as **Treatment for relapse** if complete remission was achieved but relapse occurred.
- Consolidation: Therapy given once a clinical / hematologic remission is achieved. May be given as part of a protocol to eliminate minimal residual disease (MRD).
- Maintenance: Therapy given following induction and consolidation. Given to 'maintain' the current disease status and prevent relapse / progression.
- Treatment for relapse: Therapy given to induce complete remission following relapse.
- Bridging therapy: Therapy given between apheresis and infusion. Given to 'hold over' until the infusion.
    - The disease-specific forms do not have a bridging therapy option.
        - Report this type of therapy as **Consolidation** if relapse did not occur
        - Report this type of therapy as **Treatment for relapse** if relapse occurred

Types of Therapy

Depending on the pre-infusion disease-specific forms, various types of therapy are collected.

- Systemic therapy: Delivered via the blood and distributed throughout the body. May be administered orally or intravenously.
    - Examples: Busulfan, fludarabine, thiotepa, melphalan
- Intrathecal therapy: Chemotherapy administered via lumbar puncture to treat or prevent disease in the central nervous system.
    - Examples: Triple IT, IT methotrexate, IT cytarabine
- Radiation therapy: Consists of gamma rays, high energy x-rays, electron beams, or proton beams to kill cancer cells. Radiation is either delivered as a single dose or in several treatments (fractions). Includes both treatment and palliative radiation.
    - Report both treatment and palliative radiation as a line of therapy.
        - Depending on the scenario, radiation may be reported as a separate line of therapy or in conjunction with another type of therapy.
- Surgery: Surgical treatment, resection
- Intraocular therapy: Chemotherapy administered via injection to the eye.
- Photopheresis: Removing blood from the body, exposing it to psoralen and ultraviolet light, and then reinfusing the blood.

Start and Stop Dates

Therapy start and stop dates of each line of therapy are captured on the pre-infusion disease specific forms. Use the following guidelines to report therapy start and stop dates:

- Therapy start date: Report the date when therapy began. If the start date is partially known (e.g., mid-

July 2010), use the process for reporting estimated dates .

- Therapy end date: Report the date of the final administration of therapy is reported. If therapy is administered in cycles, report the date when the last cycle was started. If the start date is partially known (e.g., mid-July 2010), use the process for reporting estimated dates .
    - If only one cycle is given, report the end date as the final administration of the drug.

Best Response to Line of Therapy

The best response (clinical / hematologic) to therapy, prior to the initiation of any new therapy is captured on the pre-infusion disease-specific form.

- Some pre-infusion disease specific forms may also capture the minimal residual disease (MRD) status.
  The first date when the best response was achieved should be reported. This date may be date during the line of therapy, or after, but prior to starting the next line of therapy.

What Not to Report

The following should not be reported on the pre-infusion disease-specific forms:

- Prior transplants
    - Including preparative regimen
- Prior cellular therapies
    - Including lymphodepleting therapy
    - The pre-infusion disease-specific forms list ‘cellular therapy’ as a line of therapy option; however, this is disabled and will be removed with future form revisions.
- Therapy given for other reason then to treat the primary disease for infusion.
    - Examples include, but not limited to: EBV, prior malignancies, new malignancies

Helpful Tips and Reminders

Progress Notes
Reviewing the following notes may be helpful to understand the treatment and disease history

- Initial Consult H&P: May provide an overview since the initial diagnosis of the primary disease for infusion until the first visit at the transplant center
- HCT / CT Consult: May provide an overview since the initial consult at the transplant center until the opinion for HCT / CT
- Admission H&P: Depending on the case, may provide an overview since the last discharge / HCT or CT consult / initial consult H&P and the current admission
- Discharge summary: Provides an overview of what happened during the most recent admission

Disease trackers
Creating disease trackers can be time consuming; however, they are very useful. Utilizing disease trackers allows the following:

- Track each disease assessment along with each therapy
    - Helps to ensure the correct best response and assessment date are accurately reported
- Allows one to identify why therapy is changing
- Provides one document, with the entire disease history and treatment, to review with the physician when there are questions

Understand Why Therapy Changed
It is important to ask why therapy changed

- Did therapy change due to a change (or lack of response) in disease?
- Did therapy change for another reason?
  The reason therapy changes will help determine if therapy should be reported as separate instances or as one instance

Section Updates:

Question Number	Date of Change	Add/Remove/Modify	Description	Reasoning (If applicable)
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Last modified: Apr 21, 2024