Guidance for DF/HCC Regulatory Staff and IRB Reviewers on Cell Therapy ICFs

Overview: Protocols involving cellular therapy products are subject to additional institutional and regulatory requirements. This information sheet provides consent form guidance and recommended language for these studies. This langauge has been previously vetted by Cell Therapy Staff at DFCI, BWH, BCH, MGH, BIDMC and has been viewed by DF/HCC IRB Chairs. Study teams are encouraged to adhere to this guidance when drafting consent forms in order to avoid delays during IRB submission and reviews. (For guidance related to other aspects of Cell Therapy ICFs such as leukapheresis and risks of receiving genetically-engineered products, please refer to "*Guidance for Leukapheresis Description and Risks for Cell Therapy ICFs*" and "*Guidance for Genetically-Modified Cell Therapy Description and Risks for Cell Therapy ICFs*".

Introduction, Point 1 – "Why am I being invited to take part in this research study?"

Example for Autologous CD19 CAR Therapy:

This research study involves screening for eligibility, collection of T cells (leukapheresis), lymphodepleting chemotherapy, infusion of Axi-cel, and follow-up visits. Axi-cel cells are a cellular therapy that involves genetic modification of your own T cells in a specialized laboratory to better recognize CD19 proteins expressed on your lymphoma cells. T cells are a part of your immune system which usually helps fight infection and prevent/fight cancers.

- **Variations** needed in this language for name of individual product, target antigen and different types of cells such as allogeneic CARs, engineered TCR cells, non-genetically modified cytotoxic T lymphocytes or NK cells, or tumor infiltrating lymphocytes. Description for HSCT (hematopoietic stem cell transplantation) will also be different.

Introduction, Point 5 – "What are the risks to participating in this study"

Example for Autologous CD19 CAR Therapy:

Cytokine Release Syndrome (CRS): A group of symptoms associated with the use of CAR T cells. CRS results from a release of chemicals that cause inflammation called cytokines into the blood circulation by immune cells following the cell therapy infusion. CRS can affect many parts of the body. CRS has generally been manageable and reversible with supportive care measures and medications, although severe or life-threatening events requiring life support (intensive care), blood pressure medications, dialysis, or ventilators (breathing machines) and fatalities have rarely occurred.

Neurologic Toxicity (Immune effector cell-associated neurotoxicity syndrome): a group of symptoms involving the function of the brain and spinal cord associated with the use of CAR T cells. The most common neurologic toxicities include headache, confusion, difficulty speaking or understanding language), and anxiety. Severe or life-threatening cases have occurred.

- **Variations** needed in this language for different cell types that may have alternate or added 2-4 key risks – e.g., risk of cerebral edema or GvHD (if allogeneic product)

Introduction, Section A – "Why is this research being done?"

Example for Autologous CD19 CAR Therapy:

This cell therapy uses your own genetically altered immune cells as an investigational cell product to treat B-cell lymphoma. A retrovirus is used as a transportation system to introduce a gene that creates a protein called a chimeric antigen receptor or CAR on the surface of your T immune cells. The CAR on your T cells is designed to bind to and help kill cells that express CD19, a molecule that is found on your lymphoma cells.

- **Variations** needed in this language for different cell types such as allogeneic CARs, engineered TCR cells, lentiviral vectors/gene editing modalities. Different language also needed for non-genetically modified cytotoxic T lymphocytes or NK cells, or tumor infiltrating lymphocytes related to numerical expansion and activation of activity during production. And combos thereof….. Description for HSCT will also be different.

Study Events:

Leukapheresis - if relevant, see separate "*Guidance for Leukapheresis Description and Risks for Cell Therapy ICFs*"

Description of cell journey, time frame, changes successful manufacturing and storage – this directly impact liability, especially for each institution's cell processing lab.

Example for Autologous CD19 CAR Therapy:

The leukapheresis product will be shipped by the Dana-Farber's Cell Manipulation Core Facility (CMCF) (*** insert site cell processing facility as relevant) directly to Kite's production facility for manufacturing of antiCD19-CAR T cells as described above. This manufacturing process takes approximately 3 weeks. Once the CAR T cells are manufactured and all safety/quality testing complete, they will be shipped back frozen to the DFCI CMCF (***), where they are stored until you are ready for your infusion.

There is a small risk that we may not initially collect enough cells to make your dose of investigational T cells or that manufacturing may not be successful in producing a product of sufficient quality to administer to you. If this is the case, your study doctor will discuss with you possibilities such as getting the investigational T cells at a lower dose or outside of this particular clinical trial, a repeated attempt at manufacturing at Kite using excess frozen cells originally collected or after undergoing a second leukapheresis procedure exactly as described above for your initial one.

Any extra cells which did not undergo modification into CAR T cells will be retained at Kite's manufacturing center for 1 year and until then may be used for re-manufacturing in the event of an initial product failure. After that period of time they may be destroyed, except for minimal stored samples required to be retained per regulatory agencies.

Once the CAR T cells have been manufactured and delivered to the DFCI Cell Manufacturing Core Facility (***) for storage and then later administration to you, it is possible that your clinical situation may have changed so that the cells are not infused into you right away. The CMCF (***) will store your cells for up to 1 year before they are discarded or returned to the sponsor/manufacturer. The sponsor may also destroy manufactured cells after 1 year, except for minimal stored samples required to be retained per regulatory agencies. You may not be informed when any of these cells are destroyed.

- **Variations** needed in this language as ever sponsor has different expiration times for various cell types. Allogeneic off-the-shelf require none of this. Cells manufactured totally within DFCI CMCF or site's manufacturing facility will have different and less verbiage.

Example for Standard of Care Stem Cell or Donor Lymphocyte Infusion Products:

At times more cells are collected from a donation than are needed to perform a transplant (or lymphocyte infusion). If your physician determines that it is preferable to administer a dose of cells that is less than the complete collection, the extra cells may be frozen and stored in freezers at your institution's cell processing facility for potential future use. After 10 years, the remaining cells may be removed IF your doctor determines that they are no longer clinically useful to you. If your donor is unrelated to you, these remaining cells will be discarded without your being notified. Alternatively, if your donor is related to you or the cells collected were your own, you will be notified and may request in writing that we transfer these frozen cellular products to another facility of your choice.

- **Variations** needed in this language will be to differentiate autologous vs allogeneic and stem cell vs mononuclear cell collections and whether if on a trial the IND holder has different time frames for stem cells/DLI cells.

Risks of Leukapheresis - if relevant, see separate "*Guidance for Leukapheresis Description and Risks for Cell Therapy ICFs*"

Risks at time of Cell Therapy Infusion:

Example Autologous CD19 CAR Therapy:

- **Infusion-related reactions** during and shortly after cell therapy infusion may include a rash, hives, fever, difficulty breathing, and low blood pressure. Although usually reversible with treatment, these can be severe or life-threatening. Risks are minimized by administration of medications such as acetaminophen and diphenhydramine prior to cell infusion.
- Your CAR T cells will be frozen and then thawed prior to infusion into you. In order to freeze and thaw them without damage, a preservative called **dimethylsulfoxide (DMSO**) is added. Side effects of this preservative may include temporary drop in blood pressure, headache, an unpleasant taste in your mouth and a disagreeable odor in the air that may last for a few days. These potential side effects are usually temporary if they occur.

- **Variations** needed in this language: fresh infusions will NOT have DMSO risk but also carry higher risk of infectious disease/bacterial transmission as no prolonged culture data. When

- using certain manufacturing/cell-selection approaches, risks of anaphylaxis to iron, murine proteins, etc. may need to be included. These same risks apply to HSCT products.

Risks Following Cell Therapy Infusion:

Example Autologous CD19 CAR Therapy:

Very Common (seen in greater than 25% of patients)

- **Cytokine-release syndrome** (CRS) is a group of symptoms associated with the use of CAR T cells. CRS results from the release of substances, called cytokines, that cause inflammation. CRS can affect many different parts of the body, and most patients will have at least some of the symptoms listed below. Severe cases requiring intensive care, blood pressure medications, dialysis, or ventilators (breathing machines) have occurred. Specific symptoms include:
    - Fever and tiredness.
    - Rapid or irregular heart rate, decreased heart function, cardiac arrest, heart muscle injury, or very low blood pressure. These events may be serious or life-threatening and require special medications or procedures to restore blood circulation, including cardiopulmonary resuscitation (CPR).
    - Shortness of breath and low oxygen supply sometimes requiring supplemental oxygen and/or insertion of a breathing tube and placement on a ventilator (breathing machine) to help with breathing.
    - Vascular leak syndrome (fluid in your bloodstream leaks out of circulation into other areas of your body).
    - Low urine output and kidney failure, sometimes requiring dialysis.
    - Stomach/liver/intestine problems including liver dysfunction. Presentation can range from abnormal laboratory values without clinical signs or symptoms to pain, nausea, and vomiting or serious and life-threatening liver failure.
- **Neurologic side effects** involving the function of the brain and spinal cord are associated with the use of CAR T cells. Most patients will have at least some of the symptoms listed below. Severe or fatal cases have occurred. Specific symptoms include confusion, difficulty speaking or understanding speech, prolonged or pronounced sleepiness, tremors (shaky hand or other body part), facial droop, seizures which may be prolonged, inability to control bladder or bowel, weakness in arms and/or legs, difficulty or inability to walk, anxiety, and dizziness. Neurologic side effects can lead to difficulty breathing and low oxygen levels, requiring insertion of a breathing tube and placement on a ventilator (breathing machine) and can be potentially life-threatening.

Other common toxicities:

- **Electrolyte/blood salt changes** (e.g., changes in sodium, calcium, phosphate, magnesium) that if severe can cause alterations in heart rhythms.
- Decrease in the number of cells that carry oxygen (**anemia**), which may make you feel tired and/or short of breath and may require a blood transfusion.
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- Decrease in the number of white blood cells (**neutropenia**), which can increase your risk of infection.
- Fever associated with a very low white blood cell count (**febrile neutropenia**).
- Decrease in the number of cells that help clot the blood (thrombocytopenia), which can increase your risk of bleeding.

Common (seen in 10-25% of patients)

- **Tumor lysis syndrome** is caused by the sudden, rapid death of cancer cells in response to treatment. When cancer cells die, they may spill their inner (intracellular) contents, which accumulate faster than they can be eliminated. This debris from the cancer cells can change the balance of the chemistry of the body. Examples of this would be: high potassium causing irregular heartbeats; high uric acid could damage the kidneys; and high uric acid sometimes leads to joint pain [i.e., gout]. We will monitor for these types of chemical changes in your body through blood tests performed at each visit. Other symptoms of tumor lysis syndrome include severe nausea and vomiting, shortness of breath, an irregular heartbeat, urine abnormalities, severe fatigue and/or joint pain.

- **B-cell aplasia:** Because of how CAR T cells work, they are expected to remove a specific type of white blood cells called B cells from your blood. B cells make antibodies to help protect you from infection. The treatment you receive may increase your risk of contracting certain kinds of potentially life-threatening bacterial, viral, and fungal infections. B cells and your natural antibodies may be very low for more than a year after treatment and may never return to normal levels. Most people who have received products like CAR T cells have needed to receive treatment to replace antibodies in their blood through intravenous immunoglobulin (IVIG) infusions, which will help protect them from the infections listed above, but will not completely eliminate the risk of contracting them

Rare (seen in less than 2% of patients)

- **Failure of bone marrow** to make blood cells including white blood cells, red blood cells, and platelets, which increases the risk of infection, fatigue/shortness of breath, and bleeding.

- **Hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS)**, which is a life-threatening disease in which white blood cells become super-activated, causing severe and widespread inflammation affecting many different parts of the body. Symptoms may include enlarged liver or spleen, rash, low blood counts, and neurologic abnormalities. This syndrome may require aggressive treatment including chemotherapy and bone marrow transplantation.

Rare (seen in less than 2% of patients)

- **Brain swelling (cerebral edema)** is an important potential risk associated with CAR T cells and brain swelling (cerebral edema) leading to death has occurred in studies involving CAR T-cell products. Symptoms may include headache, nausea, vomiting, changes in vision, severely decreased brain function that can lead to lethargy and coma (loss of consciousness), difficulty

breathing, permanent disability, and death. This may require aggressive treatment including placing a breathing tube for mechanical ventilation (breathing machine), administration of medications, or surgery to decrease the swelling or pressure. The exact cause of cerebral edema in connection with treatment of CAR T-cell products is not fully understood at this time.

- **Variations** needed in this language introduced by other cell types. Some cells like CTLs and TILs will not have much less risk of CRS and neurotoxicity. Therapies not targeting B cells will not list B-cell aplasia. Allogeneic cells will have risk of GvHD. Some sponsors state potential risk of transmission of various infectious organisms through allogeneic cells. Risks following HSCT will also be different.

Example Allogeneic Cell Therapy:

Graft versus Host Disease is a condition where the donor's immune cells (the graft or product) view the recipient's/your healthy cells (the host) as foreign, and attack and damage the healthy cells. This may cause damage to several organs including the skin, liver, and the gastrointestinal tract, among others. GvHD can be mild, moderate, or severe. In some cases, it can be life-threatening. Depending on the severity of GvHD, you may need medication designed to control the immune system to treat GvHD.

- Acute GvHD may cause skin rash, nausea, vomiting, diarrhea, yellowing of the skin and/or eyes, abnormal liver function test results, eye irritation.
- Chronic GvHD may affect many organs, including skin rash or other skin symptoms; abdominal swelling, yellowing of the skin and/or eyes, and abnormal liver function test results; dry eyes or vision changes; dry mouth, white patches inside the mouth, pain or sensitivity to spicy foods; shortness of breath or changes seen on your chest X-ray; difficulty or pain while swallowing or weight loss; fatigue, muscle weakness, or pain.

- **Variations** needed in this language introduced by other cell types. Some cells like CTLs and TILs will not have much less risk of CRS and neurotoxicity. Therapies not targeting B cells will not list B-cell aplasia. Allogeneic cells will have risk of GvHD. Some sponsors state potential risk of transmission of various infectious organisms through allogeneic cells. Risks following HSCT will also be different

Risks Associated with Receipt of Genetically-Modified Cells: e.g., viral vectors (retro, lenti, AAVs), transposons, gene-editing using mRNA, CRISPR/Cas9 or other mechanisms, induced pluripotent stem cells.

New methods of genetic manipulation are continually evolving and new risk descriptions are needed in an ongoing fashion. If relevant, see separate "*Guidance for Genetically-Modified Cell Therapy Description and Risks for Cell Therapy ICFs*"

Who will use or share protected health information about me?

- DF/HCC and its affiliated research doctors and entities participating in the research, **including affiliated apheresis collection facilities and cell processing laboratories,** will use and share your protected health information. In addition, other DF/HCC offices that deal with research oversight, billing or quality assurance