# Appendix (as Supplemental material): Consideration and requirements for the identification of qualified treatment centers for gene therapy

In order to facilitate the identification of qualified treatment centers potentially capable of practising gene therapy for the treatment of patients with β-TDT by the competent authorities, the SITE proposes a set of requirements and recommendations for suitable treatment centers, divided into three main categories:

1. ability to deliver therapy

2. pathology experience

3. instrumentation and organizational procedures.

Overall, these requirements and recommendations will show:

* whether a center meets current standards for hematopoietic stem cell transplants
* whether the staff/manager of the center has adequate knowledge of hemoglobinopathies and the treatment of adolescents and adults with β-TDT
* the consolidated experience of the center in conducting prospective experimental and observational clinical studies
* adherence to the CD34+ cell collection and processing methods consistent with FACT-JACIE standards (7th edition)
* that the center is compliant with risk management procedures as defined by FACT-JACIE standards (7th edition).

Moreover, centers should also provide specialists to discuss advantages (lack of GVHD, potential definitive cure, gene addition versus gene editing) and potential side effects of the treatment (lack of complete curative effects, loss of fertility and potential development of MDS or oncogenesis) to the patients and family members. Fertility experts, scientists, psychologists and social workers should be available to the patients to address all the questions.

## Ability to deliver gene therapy

* **Each center must meet the national mandatory requirements for peripheral hematopoietic cell transplantation.**
* **Each center must be accredited according to FACT-JACIE standards (7th edition).** 
  + This standard of accreditation is an indicator of the ability of the treatment center to comply with operating standards in terms of skills in transplantation and apheresis (consistent with European Society for Bone and Marrow Transplantation requirements and as included in the protocols of the manufacturing companies) to ensure the safety of the patient treated with gene therapy.
* **Each center must have a healthcare team properly trained in the correct management of gene therapies, based on gene addition technology and cell therapies (accreditation for therapy with immune effector cells according to FACT-JACIE standards (7th edition).**
  + In addition, the center must have *ad hoc* scientific training available, organized by manufacturing companies, in the language of the country where the center is located.
* **The center must have staff with documented experience in the staminoapheresis protocols involved in gene therapy.**
* **The center must have the skills to implement the long-term follow-up of patients treated with gene therapy as required by the European Medicines Agency (EMA) and therefore must have a data management service.**
* The center and the specialized center for hemoglobinopathies will have to carry out a long-term surveillance study aimed at monitoring patient safety for 15 years following the infusion of gene therapy and will have to disseminate the relevant data.
* **The center must adhere to the FACT-JACIE standards (7th edition) and the manufacturer's quality standards.**
  + The manufacturing company will support the quality managers at the center in maintaining the required accreditation and quality standards, and this will be verified by regular audits.

## Medical experience

* **The center has close collaboration with specialized centers for hemoglobinopathies** in order to promote better patient care and potentially to contribute to the achievement of optimal results from gene therapy**.**
* **The center must have a formally approved transplant program and perform allogeneic hematopoietic stem cell transplants in malignant and non-malignant diseases consistent with JACIE-FACT standards (7th edition).** 
  + This requirement is specified to guarantee the institutional recognition of the program, the possibility of extending the procedure to patients presenting the indication, and the allocation of adequate resources for the correct management of patients with β-thalassemia. The experience in allogeneic hematopoietic stem cell transplantation primarily in non-malignant pathologies, in particular β-TDT or sickle cell anemia, is not only an indicator of the capacity of the manager/staff of the center to administer gene therapy to these patients, but also of the on-site availability of the skills necessary to perform apheresis and infusion in hemoglobinopathies according to the approved protocols. The experience is documented in the curriculum of the Program Director and/or at least one of its senior collaborators. The center must ensure adequate patient follow-up on an outpatient basis, through internal resources or through a consolidated network with a specialized center for hemoglobinopathies.
* **The center must have experience in stem cell mobilization with the use of mobilizing agents, such as filgrastim and plerixafor.**
* **The center must be able to perform stem cell collection in selected patients using central venous catheterization, possibly after sedation for insertion of the catheter.**
* **The center must have experience in the infusion of cryopreserved stem cells according to the FACT-JACIE criteria (7th edition).**
* **The center must have a procedural system which guarantees the reinfusion of the cryopreserved cells within a timeframe of <30 minutes per bag.**
* **The center has resources to make further recommendations for gene therapy.** 
  + The center is aware of the possible need to extend the treatments offered in terms of dedicated space and resources for the gene therapy to ensure timely access for potentially eligible patients.
* **The center has (either internally or through agreed access) the necessary pharmacological skills to titrate treatment with myeloablative conditioning agents.** 
  + Experience in the use of busulfan as a myelosuppressive agent is required.
* **The center has direct access to intensive cardiovascular care unit (CICU).**

## Instrumentation and organizational procedures

### 3.1 Instrumentation

**Apheresis equipment.** The center must have one of the following specific pieces of equipment: Spectra Optia® Apheresis System, Fresenius Kabi Amicus® Separator or COBE® Spectra Apheresis System. The apheretic collection must be consistent with the requirements that guarantee the quality of the cells collected necessary to produce the gene therapy product as specified by the manufacturers**.**

**Equipment and space for the storage of hematopoietic cells and gene therapy products.** The center must have the following:

* containers suitable for storing cells at between 1°C and 10°C, with a temperature monitoring system equipped with an audible alarm (in case cell collection by apheresis is carried out on two consecutive days).
* a device that can store the gene therapy product in liquid nitrogen in the gas phase with automatic filling with centralized temperature monitoring for the correct conservation of genetically modified organisms; furthermore, the device must be able to contain the product box used as specified by the manufacturer; sufficient space must be available to ensure adequate long-term conservation of the rescue cells and their maintenance must comply with specific procedures, so that they can be used in emergency situations.

**Labeling and shipping.** The center must be able to create labels with the unique identification number of the donation in compliance with the FACT-JACIE standards (7th edition) and maintain operational compliance with the EU directive 2015/565 regarding the creation of the Single European Code (SEC).

**IT systems, tools and portals for programming and traceability.** The center must have an IT system that ensures patient traceability and data collection in compliance with current regulations; the IT system must be able to integrate with the tools and portals of programming and traceability of the producing companies to guarantee the correct and safe delivery of gene therapy.

### 3.2 Organizational procedures

* **Collection of the starting material to produce the drug.** The center must ensure that the patient's CD34+ cell collection is carried out in an apheresis center that can follow the protocols shared with the manufacturing companies, certifying their competence in performing apheretic collection and maintaining the fundamental quality standards for the collection of an adequate quantity and quality of cells to start the production of the drug.
* **Minimum experience for staminoapheresis:** it is essential that the center has performed at least 50 staminoapheresis per year in the last three consecutive years. (Note that the term ‘staminoapheresis’ refers to a patient, not the procedure.)
* The center must guarantee compliance with a schedule for the collection and shipment of hematopoietic cells functional to production within the times suggested by the manufacturer in order to ensure that the quality of the cells is preserved. In this context, it should be noted that the cells collected by apheresis have an average life of 48 hours, therefore active communication between the center and the specialized laboratory is required to ensure timely cell manipulation and production of the gene therapy product. To coordinate this, it is strongly recommended that an administrator (comparable to the CAR-T manager involved in coordinating therapy with immune effector cells) is appointed.
* The center must comply with an organizational system for the collection of the patient's hematopoietic cells, to allow a possible second apheresis on the day following the first cell collection in order to collect the minimum quantity of cells necessary for the correct execution of gene therapy.
* **Shipping of starting material for drug production.** The center must use the courier and the shipping method specified by the manufacturer for transport to and from the cell manipulation site to ensure that the quality of the cells is preserved.
* **Hospitalization.** The center must be organized in such a way as to guarantee the patient's stay after infusion of the product for 3–6 weeks in an adequate and dedicated environment to monitor correct implantation. If necessary, the center must also be able to accommodate re-admission of the patient for further follow-up procedures/tests after discharge.
* **Reporting of adverse events.** The center must be able to report any adverse events, procedural deviations, exceptions and other events relevant to the drug as per the national pharmacovigilance system and in compliance with the FACT-JACIE standards (7th edition) and those of the drug producer.
* **Welcome for patients and their families.** The center must put in place an adequate reception system for patients and their families, even if they are not of Italian nationality, using cultural mediators when necessary and providing social aid to support the patient and their family in an auxiliary infrastructure (e.g. to manage the possible housing needs of the patient’s caregivers/family if they are of a different nationality).