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COLLECTION OF LYMPHOCYTES BY APHERESIS

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ABSTRACT

The first step in the manufacturing of cell therapy products is the collection of cells from donors or patients. This point should be given special attention by all professionals involved in the development of these therapies because it is critical to guarantee the quality of the final product. Lymphocytes, especially T-cell lineage, have been used for treatment in a large number of pathologies, including oncological and infectious diseases, especially after approval by regulatory agencies in several countries for the use of Chimeric Antigen Receptor Therapies (CAR T). This article describes the steps for the procedure of collecting lymphocytes by apheresis, defining indications and contraindications as well as the planning and preparation measures for the procedure.

Keywords: Lymphocytes. Blood Component Removal. Immunotherapy, Adoptive.

OBJECTIVE

Describe the steps for the procedure of collecting lymphocytes by apheresis. Define indications and contraindications as well as planning and preparation measures for the procedure.

INTRODUCTION

The first step in the manufacturing of cell therapy products is the collection of cells from donors or patients. This point should be given special attention by all professionals involved in the development of therapies because it is critical to guarantee the quality of the final product[1].

Unlike the collection of cells for hematopoietic progenitor cell transplantation, in which there is a possibility of collection by apheresis of peripheral blood or directly from the bone marrow with its well-known risks, benefits and preparation of the donor, cell collection for other types of cell therapy, especially to produce CAR cells (chimeric antigen receptor), must be done by apheresis, however, the ideal procedure, the quantitative and qualitative characteristics to be achieved for the collected product, as well as the risks specifically related to this type of procedure are less known[1].

The apheresis procedure involves the application of a centrifugal force to a continuous or semicontinuous blood flow so that the different cellular components and plasma can be separated by density difference[2].

The apheresis equipment used to collect mononuclear cells differs slightly in the programming and interaction mode between the operator and the equipment, and in their cell separation technologies with Spectra Optia (Terumo BCT) equipment being the most frequently used in the United States, and COM.TEC equipment (Fresenius HemoCare) the mostly used in Europe[3,4].

Lymphocytes, especially T-cell lineage, have been used for treatment in a large number of pathologies, including oncological and infectious diseases, especially after approval by regulatory agencies in several countries for the use of Chimeric Antigen Receptor Therapies (CAR T) [5].

During the centrifugation procedure the mononuclear cells, including lymphocytes, are located between the erythrocyte and polymorphonuclear layers, which are denser, and the platelet layer, which is less dense. Thus, it is possible to return to the donor the cells that are not of interest to the collection and

store the cells of interest containing a small number of other cell types[4,6].

Most studies and commercial products that use lymphocytes as a starting cell for the manufacturing of cell therapy products use autologous cells, therefore interest in the use of allogeneic cells has grown[7], for this reason the article will focus on this type of procedure, however the interest in the use of allogeneic cells has grown and some relevant information regarding this type of donor will be presented separately.

For the collection of lymphocytes intended for the manufacture of CAR T, the donor does not need to be stimulated with growth factors, but there is still little knowledge about the clinical and technical factors that influence the results of the collection, as well as on the methods for optimizing the procedure, therefore there is much to be studied in this area[8].

We know that not all experience gained in the collection of hematopoietic progenitors can be transferred directly to the collection of mononuclear cells, mainly due to the fact that immobilized donors, for the most part, have low leukocyte counts often making the selection of target cells challenging.

The procedure for collecting lymphocytes from allogeneic donors for the infusion of lymphocytes from the donor after bone marrow transplantation is the procedure that most resembles that of the collection of lymphocytes for the production of cell therapy products. However, as most patients involved in studies and treatments with CAR T use autologous lymphocytes, these donors often have intense secondary lymphopenia related to the treatment, and this may also be associated with the presence of circulating blasts, which makes the cell separation procedure more complex, and may result in less uniform collection products[8,9].

PROCEDURE

Indications and contraindications

Patients or allogeneic donors, who have an indication of lymphocyte collection by apheresis for the manufacture of cell therapy products, and who have signed the form of the terms of free consent are indicated for the procedure.

Autologous donors, because they are patients, should have their clinical conditions evaluated on a case-by-case basis to measure the risk-benefit ratio. The fitness for the apheresis procedure should be discussed at the time of indication of CAR T cell treatment. Comorbidities such as severe heart and liver failure, in addition to ischemic heart disease with recent manifestation, may contraindicate the apheresis procedure, but this decision should be made by the physician responsible for the apheresis procedure together with the team responsible for treating the patient.

3.2 Necessary human resources

The apheresis procedure should be performed by a trained and qualified health professional for the procedure and, due to the frequent need for central venous catheter manipulation, it is advisable that the professional be a nurse, but this is not a requirement.

Moreover, a doctor, preferably a hematologist or hemotherapist, experienced in apheresis procedures, and who is technically responsible for the procedure is required.

Pediatric care should preferably be performed in an environment with a pediatrician available to care for any complications.

3.3 Minimum requirements for the procedure

Team trained to perform the procedure

Apheresis equipment available

Physical space suitable for performing an apheresis procedure

Donor approved for the procedure: attention to signs of recent infection, especially in the last 24 hours, and blood count results from the day of collection mainly for autologous donors. Be alert to the need for red blood and platelet transfusion before the start of the procedure.

3.4 Material

- Disposable kit for mononuclear cell collection (suitable for the equipment that will be used)
- Anticoagulant solution
- Saline
- Skin or catheter asepsis material (sterile gloves, gauze, alcohol, or chlorhexidine solution).

3.5 Pre-and post-procedure guidance

Pre-procedure:

Fasting is not required of the donor whose peripheral venous access is suitable for collecting by apheresis. On the contrary, they should be instructed to eat before the beginning of the procedure. It is recommended that the donor attend the collection accom-

panied by someone, or that at least someone can collect them after the end of the procedure in cases of outpatient collections. For those who require central venous access, it is important to inform the appropriate fasting time, if necessary, and the flow to catheter implantation.

Post-procedure:

Avoid performing physical exertion in the first 24 hours after donation. In the case of donors who received a central venous catheter only for the procedure, the catheter should be removed as soon as it is confirmed that the collected cellular dose has reached the target. After catheter removal, a compressive dressing should be applied appropriately to the site where the catheter was implanted, and the donor should remain at rest for at least 60 minutes to avoid bleeding at the site. For autologous donors, the medical team that is responsible for treating the patient should decide on the removal or maintenance of the catheter.

3.6 Description of the procedure

The institution should create a notification flow of donors who are candidates for the collection of lymphocytes by apheresis to manufacture cell therapy products for the hemotherapy team that will perform the procedure. Preferably, this request should be formalized through a signed document that, at minimum contains the patient identifiers and the target cells to be collected. Based on this information, the team responsible for the collection should start the procedure planning process.

Venous access:

Adequate venous access is essential for performing the procedure and the possibility of peripheral venous access should be accessed by a trained team.

In case there are no conditions for collection by peripheral venous access, the implantation of a central venous catheter must be planned.

For adult patients, a catheter with a caliber between 10 and 13.5Fr usually provides adequate flow, and the choice of using tunneled or non-tunneled catheters should take into account the planned length of catheter permanence, with the tunneled catheters being more suitable for patients who will use it to receive medications after the collection, and non-tunneled catheters more suitable for patients who will use it only for the collection procedure[2].

The experience of the team that will perform the implant should be taken into consideration for the catheter implantation site. But as a general rule, short-term catheters, should be implanted in the femoral region due to the lower risk of complications related to local hemorrhage[2].

Proper planning for venous access is important because failure in this process can lead to significant delays in collection, which can have a major impact on cell manipulation and transport logistics, as many manufacturing laboratories require a maximum time between collection and the start of cryopreservation, and others require cells to arrive fresh for manufacture.

Procedure planning:

Another important point of attention during the procedure planning is the clinical assessment of the donor and the sample collection to perform the screening for transfusion-transmissible infectious diseases.

In the case of autologous donors, the assessment can be summarized as an aptitude assessment of the apheresis procedure[10].

Mandatory laboratory tests to be performed on cell donors for advanced cell therapy products by current legislation in Brazil are:

- Hepatitis C: anti-HCV antibody and NAT for HCV

- Hepatitis B: HBsAg, anti-HBc total with differentiation of IgG and IgM or just IgG and NAT for HBC

- HIV: anti-HIV (subtypes 1 and 2) and NAT for HIV

- HTLV: serology for HTLV 1 and 2

- Chagas disease: serology for Chagas disease

- Syphilis: one treponemic or non-treponemic test

Carrying out NAT tests is not mandatory for autologous donors if handling and infusion takes place with fresh cells and there is no risk of cross-contamination during storage.

Testing for plasmid or plasmid antigens may also be required if the donor lives or travel to a malaria-endemic region in the last 12 months.

RDC 508/21 authorizes the use of an autologous donor product regardless of the test that is altered, as long as the patient's physician is aware of this alteration, however manufacturing laboratories may have their own criteria for the inability of the donor that may be stricter than national legislation, therefore, in these cases, it is recommended that screening tests for infectious diseases be carried out before the day

of cell collection, as the product may be considered unfit for use after it has already been collected.

It is worth mentioning that the current legislation in relation to cell therapy products (RDC 508/2021) cites that the screening for infectious diseases for the collection of cells other than hematopoietic progenitor cells obtained for the purpose of perform conventional transplantation must be carried out until 7 days before or 7 days after the day of collection. Ordinance 158 /2016, which defines the technical regulations for hemotherapy procedures, mentions that these tests for the collection of lymphocytes must be performed up to 72 hours before the procedure.

Other tests to determine the donor`s fitness are not a consensus among the services, being that *the European Society for Blood and Marrow Transplantation* (EBMT) indicates that hemoglobin levels should be higher than 8g/dL, total leukocytes above 1,000cells/mm3, lymphocyte count above 200 cells/mm3, platelet count greater than 30,000/mm^3, and the ejection fraction of the left ventricle should be greater than 40%[3].

Selection and determination of donor fitness:

Each service must have a POP describing the acceptable selection criteria and relevant assessments to define the donor's fitness, and these criteria may vary depending on the laboratory that will manufacture the cell therapy product.

It is important to highlight that cells that need to be exported for manipulating, or products manipulated abroad that are imported for use in Brazil must meet the legal requirements of both countries.

It is also important that after determining the fitness of the donor, he or she must be informed about the procedure, answer any questions that they may have, and that the terms of free consent form be applied, and TCLE clarification given regarding the cell collection procedure.

The TCLE should contain, at a minimum, information on the procedure for collecting cells by apheresis, risks related to the procedure, laboratory tests to which the donor will be submitted, the purpose of cell collection, and authorization of the donor for access to the team that will use the cells for manufacture to clinical and laboratory data, authorization for the storage of cell aliquots, blood and/or plasma for future tests that may be necessary, as well as the possibility of withdrawal at any stage of the process, and when it fits, what are the consequences of such withdrawal.

Special donors:

Pediatric donors

Children, especially those under 25 Kg, often require central catheter implantation. A diameter of at least 7Fr is suitable for the procedure, and unless the catheter is needed for use at other stages of treatment, a femoral implantation is recommended.

If the donor or patient is under 18 years of age, the TCLE must be signed by the parents or legal guardian.

Allogenic donor

According to RDC 508/21, allogeneic donors must be clinically evaluated and released according to criteria similar to those used for releasing blood donors.

If the donor does not have peripheral venous access compatible with the procedure, central venous catheter implantation is allowed, although not recommended, and the preference is for implantation in the femoral region performed by a vascular surgeon with experience in central catheter implants.

Allogeneic donors must perform all the tests for detecting infectious diseases mentioned for autologous donors, in addition to serology for cytomegalovirus (CMV) with titration of total antibodies + IgM or IgG + IgM and the pregnancy test is mandatory and must be performed within, maximum, 7 days before the day of the procedure.

Although the acceptance criteria for donors with altered/positive serology are different between laboratories that manufacture cell therapy products, RDC 508/21[10] says that donors are unfit for allogeneic donation: with HIV or HTLV positive test, HBsAg non-reactive with anti-HBc reactive (unless the donor also has anti-HBs reactive), HBsAg reactive and/or NAT positive for virus B, anti-HCV reactive and/or NAT positive for Virus C, or with a positive test for Trypanosoma cruzi.

Execution procedure:

On the day of collection, the correct identification of the patient and the bag should be a point of special attention.

According to general rules of safe identification, at least 2 identifiers should be used, and preferably conferred positively with the donor, i.e., the donor himself must say the two identifiers (e.g., full name and date of birth).

The bag should also be identified with a specific numbering per procedure, preferably using ISBT

encoding or, in case the service does not use ISBT encoding, a single, sequential numerical, or alpha-numeric code of the service. Some cell therapy product manufacturing laboratories also provide a specific identifier for the patient, and the bag. A secure identification procedure must be defined by the institution for safe identification, and the procedure should be defined by the institution, as later on no other type of identification check will be possible during the transportation, manufacturing, and infusion processes.

Ideally, the identification of the bag that will store the product should be done after the assembly of the disposable system of the apheresis equipment, immediately before the beginning of the procedure, and after conferring the donor`s identification to avoid any change of identification of the bag in case there is more than one patient being submitted to cell collection on the same day, or in the same service.

The procedure must be performed in apheresis equipment with a validated program for the collection of mononuclear cells, and there is diverse equipment available in the national market. All available equipment can be used with advantages and disadvantages being that the experience of the service in using the equipment is a factor that should be taken into consideration when choosing the equipment to be used. The table in Annex 2 shows some of the leading manufacturers of apheresis equipment as well as a comparison of their main characteristics.

Technically, the procedure is very similar to the collection of donor lymphocytes for infusion after allogeneic transplantation, and, to date, neither the companies that produce the apheresis equipment nor the manufacturing laboratories have defined a specific protocol for the collection of lymphocytes for the collection of T cells for cell therapy, therefore each service must validate its process based on the information provided by the manufacturer of the apheresis equipment for the collection of lymphocytes.

The best way to validate the collection process is the systematic calculation of the collection efficiency of the procedures performed in the service followed by the comparison with benchmarks. In addition, the achievement of collection objectives is also a very important indicator, since, in practice, this is the objective of the entire procedure.

A collection efficiency greater than 40% is generally considered adequate but may vary depending on the type of equipment used as showed in Annex 2[3].

The efficiency calculation is obtained using the following formula:

Collection efficiency: total CD3+ cell count in the bag /(CD3+ peripheral cell count per litre x volume of processed blood in litres) x 100

When the average collection efficiency of the service is known, or, ideally, the efficiency of the equipment being used, it is also possible to calculate the volume to be processed to reach the volume of target cells for the patient. However, not all laboratories require a minimum target of CD3+ cells or lymphocytes, some request that a certain blood volume be processed according to the weight and peripheral lymphocytes count of the donor or patient, and others request a minimum volume of mononuclear cells.

Thus, each service must determine its protocol for calculating the volume to be processed to reach the target requested by the laboratory that will manufacture the product that will be collected.

Although the procedure can be performed in patients with an absolute count of lymphocytes in peripheral blood below 100 cells /mm^3 the probability of obtaining a number of lymphocytes that is sufficient for the manufacture of the cell therapy product greatly increases when this value is above 500. However, most adult patients with peripheral lymphocyte count equal to or greater than 200/mL can obtain the minimum required amount of cells T for manufacturing in only one collection procedure with the processing of 3 to 4 blood cells and in cases where a collection is not sufficient, it is possible to perform a second collection on the following day.

In addition, to avoid the adverse effects related to the accumulation of exposure to chemotherapeutics, either in the reduction of T-cell production and in the quality of these, the collection of cells should be scheduled, whenever possible, before the start of rescue chemotherapy. Where such a procedure is not possible, a minimum interval between the administration of rescue medications and collection should be carefully considered.

Before the initiation of an apheresis procedure, the

donor must be clinically assessed for vital signs and medical solicitation documents for the procedure, determination of the fitness of that donor, and a consent form must be checked for the necessary content and signatures. Any lack of documentation or incorrect information should result in a temporary suspension of the procedure until the matter is resolved.

The donor must also be reminded about the donation procedure, possible symptoms related to the procedure, and any inquiries should be clarified before starting the procedure.

After initial checks, the procedure should take place according to the guidelines provided by the manufacturer of the equipment used for the collection of lymphocytes and the final liquid balance must be as close to zero as possible, and the positive balance must not exceed the limit of 20% of the total blood volume of the patient[4].

Anticoagulation:

For the apheresis procedure, anticoagulation is a primordial process and ensures the quality of the collected product. In general, a 1:10 to 1:12 rate of citrate is sufficient to promote adequate anticoagulation. Typically, with this anticoagulant ratio, electrolyte replacement is not required if processed up to 2 times the total blood volume. If a lower ratio is required, which results in greater use of citrate, the processing of higher blood volume, or in children (especially those below 20 kgs) prophylactic calcium replacement may be recommended and should be part of the protocol developed by the service.

Many laboratories manufacturing cell therapy products discourage the use of heparin as it can interfere with cell culture, therefore, anticoagulation should be discussed with the laboratory that will manufacture in cases of patients with hypersensitivity to citrate, or patients with severe renal or liver failure.

Collection objectives:

The coloration of the collected product should be light salmon, with a hematocrit expected between 2-3%[7].

The minimum and ideal cellularity for collection vary according to the laboratory that will do the manufacturing, however, minimum cellularity of $0.5x10^9$ CD3+ cells and target cellularity of $2x10e^9$ meet most of the available manufacturing protocols.

And at the end of the apheresis procedure, it must be ensured that the bag containing the collected product is correctly identified. Moreover, some laboratories request that milking pliers not be used in the bag segment after sealing and separating the apheresis kit.

Records:

Always pay attention to ensure that all data related to the procedure were carefully and adequately recorded on its form, or on an electronic system containing, at a minimum, the donor`s identifiers, bag number, date, and time of start and end of the procedure, and the volume of the collected product. An example worksheet where the procedure data is recorded can be viewed in Annex 1.

CRITICAL POINTS AND PROCESS RISKS

Adequate evaluation of venous access so that the central access is not indicated beyond what is necessary, but also not running the risk of starting the procedure with peripheral access, which can prove to be inadequate.

- Correct identification of the collection bag.

- Risk of secondary hydro-electrolytic disorders in the use of citrate-based anticoagulants.

- Risk of anemia and thrombocytopenia, during and after the procedure.

- Risk of hypothermia, due to extracorporeal circulation in young children.

STANDARD OF PRACTICE

The instituition must determine its efficiency goal according to the equipment used, as well must define goals in relation to the number of procedures necessary to achieve the collection objective.

The rates of serious adverse events (grade 3-4, classified according to CTC-NCI) should be lower than 1% of the procedures.

PERIODICITY OF TRAINING OR ASSESSMENT OF COMPETENCIES

The instituition should define the basic competencies for hiring the professional who will work in the apheresis sector. After hiring, it is necessary to define a procedure that includes the initial training and the methodology in the preparation of a professional to perform the function. Furthermore, the service quality program must define a regular training and upgrading program.

The professional qualified to perform the apheresis procedure must be a trained healthcare professional that is qualified to do this task, due to the frequent need for manipulation of central venous catheters. Preference should be given to nursing professionals, but such training is not mandatory.

We suggest the following steps in the initial training:

Observation of at least 2 collections by apheresis after reading the service's POP, followed by a written assessment to record the effectiveness of the training.

Performance of 3 to 5 procedures under supervision, and if the professional and supervisor are sure that the professional is fit, free to work on their own.

Training routine should be defined, at least annually with a recorded or registered participation of professionals.

SUGGESTED QUALITY INDICATORS

Collection efficiency

Average number of procedures per patient to reach the collection target

Rate of procedure-related adverse events

ANNEXES

Annex 1. Example of worksheet for recording the cell collection procedure by apheresis.

GRUPO GESTOR EM SERVIÇOS DE HEMOTERAPIA

FORMULÁRIO DE COLETA DE CÉLULAS POR AFÉRESE

Local de Coleta: _____ Data:___/___/_____ Nº Sessões:_____
Início:____:____ Temperatura Ambiente:_____°C Umidade Ambiente: _____
Término:____:____ Temperatura Ambiente:_____°C Umidade Ambiente: _____

Tipo de Coleta: ( ) Autólogo ( ) Alogênico

Se Alogênico:
( ) Aparentado ( ) Não Aparentado
Nome do Receptor:_____
Data de Nascimento:___/___/___ Peso:_____ Altura:_____Sexo:_____ABO/RH:_____
Diagnóstico/Indicação:_____

1. Dados do Doador

Nome: _____
Atendimento:_____ Leito:_____ Data de nascimento:___/___/_____
Convênio:_____ Nº: _____
Sexo:_____ Peso:_____ Altura:_____ VST: _____ ABO/RH:_____
Diagnóstico/Indicação:_____
Dupla Checagem na Identificação do Doador? ( ) Sim ( ) Não Responsáveis: _____
Acesso Venoso: ( ) Periférico ( ) Central Tipo:_____
Se Cateter: ( ) Apto ( ) Não Apto Checado por: _____

2. Exames Laboratoriais

Data dos Exames: ___/___/_____ CD34+/CD3+ Pré:_____ %:_____ Ht:_____
Hb:_____ Leucócitos: _____ Plaquetas:_____ Cai:_____ K:_____Mg:_____
Uréia:_____ Creatinina:_____ Outros:_____

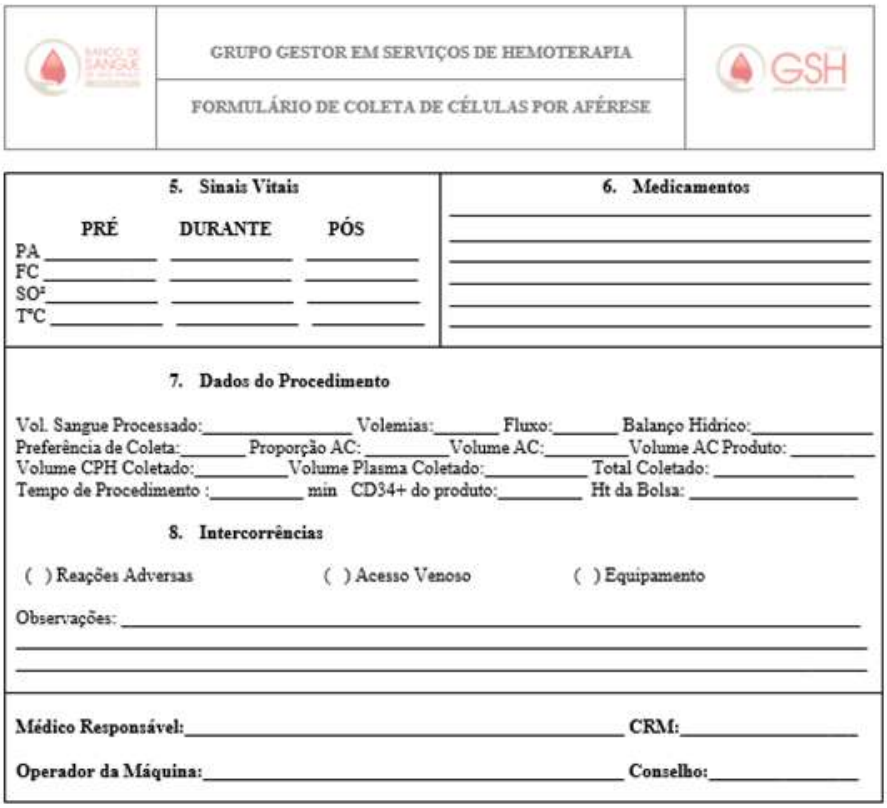
3. Mobilização

G-CSF Data de início:___/___/_____ QT Prévia: ( ) Não ( ) Sim - Data de início: ___/___/_____
Plerixafor: ( ) Não ( ) Sim – Data de início: ___/___/_____
Observação:_____

4. Materiais e Equipamentos

Equipamento: ( ) MCS+ ( ) Cobe Spectra ( ) Optia
Nº do Equipamento:_____Higienizado em:___/___/_____Responsável:_____

Kit:_____ Fabricante: _____ Lote: _____Validade:_____
Anticoagulante Fabricante:_____Lote:_____Validade:_____
Soro Fisiológico Fabricante:_____ Lote: _____Validade:_____
Bolsa Térmica – Identificação:_____Higienizada em: ___/___/_____Responsável: _____



GRUPO GESTOR EM SERVIÇOS DE HEMOTERAPIA

FORMULÁRIO DE COLETA DE CÉLULAS POR AFÉRESE

5. Sinais Vitais

	PRÉ	DURANTE	PÓS
PA			
FC			
SO²			
T°C			

6. Medicamentos

7. Dados do Procedimento

Vol. Sangue Processado:_____ Volemias:_____ Fluxo:_____ Balanço Hídrico:_____
Preferência de Coleta:_____ Proporção AC: _____Volume AC:_____Volume AC Produto: _____
Volume CPH Coletado:_____Volume Plasma Coletado:_____ Total Coletado: _____
Tempo de Procedimento :_____ min CD34+ do produto:_____ Ht da Bolsa: _____

8. Intercorrências

( ) Reações Adversas ( ) Acesso Venoso ( ) Equipamento

Observações: _____

Médico Responsável:_____ **CRM:**_____

Operador da Máquina:_____ **Conselho:**_____

Annex 2. Main models of apheresis equipment and their performance characteristics (adapted from Cellular Therapy: Principles, Methods, and Regulations)[4]

Equipament	Collection process	Extraction flow rate (mL/min)	Extracorporeal Volume	Platelet reduction after procedure (%)	Average collection efficiency for MNC (%)
Spectra Optia (Terumo BCT)(11)	Continuous blood flow, continuous collection	40-80	191mL*	13-42%	60%
COM.TEC (Fresenius)	Continuous blood flow, cyclic collection	NI	130mL	22-50%	21,4%
Haemonetics (MCS)	Intermittent blood flow, cyclic collection	20-30	480mL	39-46%	NI

* Typical extracorporeal volume147mL, can reach 191mL
NI: not informed by the manufacturer

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