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FULL-LENGTH ARTICLE
Manufacturing

Recommendations for procurement of starting materials by apheresis for advanced therapy medicinal products

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ABSTRACT

Activities involved in the production of certain advanced therapy medicinal products (ATMPs) require standardized approaches to mononuclear cell procurement to ensure the highest product quality, safety and process efficiency. These aims must be achieved while meeting regulatory and accreditation requirements for the procurement of mononuclear cells as starting materials. Mononuclear cells constitute the starting materials for many ATMPs, and this article sets out recommendations for procurement by clinical apheresis, addressing the variation among existing working practices and different manufacturers' requirements that currently poses a challenge when managing multiple different protocols.

Introduction

Advanced therapy medicinal product (ATMP) manufacturing must produce safe and high-quality products for clinical use. However, ATMP quality and safety are dependent on the provenance of the supply chain from donor or patient to final medicinal product, and significantly impacted by quantitative and qualitative variation in the starting material. Such variation can be biological and somewhat unavoidable as a result of the underlying diagnosis, therapeutic treatment and current health of the patients and donors. Conversely, procedural variability may be mitigated by standardization.

To achieve these aims, the processes at each stage of the ATMP supply chain must be controlled and standardized wherever possible to ensure quality and safety, improve process efficiency and reduce the risk of error while meeting regulatory and accreditation requirements. Over 50 clinical apheresis units across the UK are involved in

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mononuclear cell (MNC) procurement, largely for hematopoietic stem cell transplantation, and operate under a Human Tissue Authority (HTA) license. In the UK, ATMP starting material procurement by apheresis can be accomplished under HTA Tissue Establishment or Medicines and Healthcare products Regulatory Agency Blood Establishment licensure; in clinical settings, collection is normally made under an HTA license in accordance with Human Tissue (Quality and Safety for Human Application) Regulations 2007. In addition, most clinical apheresis units have Joint Accreditation Committee of the International Society for Cell & Gene Therapy and European Group for Blood and Marrow Transplantation (JACIE) accreditation. However, variation in working practices among clinical apheresis units causes problems for manufacturers that require control of the quality of starting materials through standardized processes. Similarly, variation in manufacturers' requirements poses challenges for clinical apheresis units, as managing multiple protocols for the same starting material leads to duplication, inefficiency and increased risk of non-compliance for stakeholders. This systematic problem is likely to worsen over the coming years, as an increasing range and larger number of starting materials are required to support pivotal trials and clinical adoption of ATMPs. With limited control over patient- and donor-related factors that impact cell collection quality, the focus must be on control and standardization of the collection process and collaboration with ATMP manufacturers.

This article presents the results of the UK Review and Recommendations on the Procurement of Starting Materials by Apheresis for ATMPs, initiated as part of the UK Advanced Therapy Treatment Centre Network Standard Approach to ATMP Tissue Collection project (https://www.theattcnetwork.co.uk/). The objective was to bring together stakeholders from across the academic, commercial and health care ATMP communities to agree on standardized approaches to MNC procurement [1].

Methods

A working group of members from affiliated organizations performed a survey of JACIE-accredited clinical apheresis units in the UK to identify current practices and make recommendations for guidance on MNC collection settings and endpoints. Information was gathered via questionnaires, online surveys and telephone calls. The survey looked at practices around MNC collections, starting materials for ATMP manufacturing, software and procedures used in apheresis. Issues related to quality management, audits and regulatory compliance were also reviewed. The survey questions and summary responses are provided in Table 1 for reference [1]. The responses to the survey were analyzed and reviewed and recommendations drafted by the guideline working group (listed as the authors) and circulated widely to relevant members of the UK community, including clinical apheresis units, manufacturers and regulators, for comment prior to final drafting.

Results

The survey was sent to 36 clinical apheresis units, of which 29 (80%) responded, including most major units, accounting for approximately 70% of the yearly MNC collections in the UK. The results included feedback from the nine initial UK National Health Service sites that currently provide commissioned chimeric antigen receptor (CAR) T-cell products, clinical apheresis units that have applied for or are accredited by JACIE and clinical apheresis units that undertake starting material collections for clinical trials. Non-responding clinical apheresis units carried out either small or very small numbers of collections and mostly performed autologous hematopoietic stem cell collections only.

Donor screening

All procurement must minimize risk to the patient/donor and starting material and occur only in areas that minimize the risk of microbial

Table 1
SAMPLE project questionnaire.

1. Please enter the name of your institution
2. Are you currently collecting cells for ATMP manufacturing for either trial or commercial products: Yes (10), No (11)
   a. If yes, please state whether for trial (3), commercial (2) or both (5)
   b. If yes, please give detail of cell types requested by the trial or commercial organization
   c. If yes, please give detail of what type of ATMP is being manufactured
3. Do you use MNC program: Yes (21), No (0)
   a. Please select procedure(s) that you use MNC program for (please select all that apply): PBSCs (20), DLI (14), lymphocytes for immuno-oncology products (10), mononuclear cells for other ATMPs (3)
   b. If mononuclear cells for other ATMPs, please specify
4. Do you use both MNC program and CMNC program: Yes (5), No (16)
   a. If yes, please specify how the use of a specific program is determined
5. What starting inlet:AC ratio do you routinely use for PBSCs, DLI, lymphocytes for other immuno-oncology products and mononuclear cells for other ATMPs
   a. If you entered a ratio for lymphocytes for immuno-oncology products (e.g., CAR T cells), is this dependent on protocol: Yes (3), No (5), N/A (13). If yes, please give a ratio range.
   b. If you entered a ratio for mononuclear cells for other ATMPs, is this dependent on protocol: Yes (2), No (2), N/A (17). If yes, please give a ratio range.
6. What adjustments might you routinely make to inlet:AC ratio and why (e.g., for small body weight)
7. Do you use any other AC in addition to ACD-A: Yes (1), No (20). If yes, please give details regarding the type of AC, its dosage, how it is administered and why it is used.
8. Do you have a minimum and/or maximum collection volume requirement for PBSCs, DLI, lymphocytes for other immuno-oncology products and mononuclear cells for other ATMPs
   a. If you entered volume requirements for lymphocytes for immuno-oncology products (e.g., CAR T cells), do they vary according to the manufacturer's protocol: Yes (4), No (2), N/A (15)
9. What endpoint is used for procedure settings (please state value as ×TBV or time in minutes for PBSCs, DLI, lymphocytes for other immuno-oncology products and mononuclear cells for other ATMPs)
   a. If you entered an endpoint for lymphocytes for immuno-oncology products (e.g., CAR T cells), is it dependent on the manufacturer's protocol: Yes (6), No (2), N/A (1)
   b. If you entered an endpoint for mononuclear cells for other ATMPs, is it dependent on the manufacturer's protocol: Yes (6), No (2), N/A (1)
10. What is the AC reinfusion rate used for PBSCs, DLI, lymphocytes for other immuno-oncology products and mononuclear cells for other ATMPs (please state value as mL/min per liter of TBV)
11. What adjustments might you routinely make to AC reinfusion rate and why (e.g., for small body weight)
12. If using CMNC program, what collect rate is used for PBSCs, DLI, lymphocytes for other immuno-oncology products and mononuclear cells for other ATMPs
    a. If you entered a collect rate for lymphocytes for immuno-oncology products (e.g., CAR T cells), is it dependent on the manufacturer's protocol: Yes (2), No (0), N/A (19)
    b. If you entered a collect rate for mononuclear cells for other ATMPs, is it dependent on the manufacturer's protocol: Yes (1), No (2), N/A (18)
13. What adjustments might you routinely make to collect rate and why
14. If using the MNC program, what chamber flush and chase volumes are used for PBSCs, DLI, lymphocytes for other immuno-oncology products and mononuclear cells for other ATMPs
15. What adjustments might you routinely make to chamber and flush volumes if using the MNC program and why (e.g., to increase/decrease the collection volume)
16. How are machine settings/endpoints determined: your organization's policy (16), the engineer (5), as part of the machine validation (7), manufacturer's or trial protocol (7), other (3)
17. Are settings adjusted during procedures: routinely (10), occasionally (9), if manufacturer's protocol allows (0), never (2). Please give further details of any adjustments made.
18. Is there any negotiation around endpoints/machine settings with the manufacturer or trial group: Yes (2), No (7), N/A (12). If yes, please provide examples (if possible) of any specific endpoint differences agreed to.
19. Which of the following pre-procedure patient/donor information do you routinely record (please select all that apply): diagnosis (21), white cell count (21), weight (21), TBV (21), platelet count (21), white cell differential (15), hematocrit (20), CD34 count for PBSCs (21), CD3 for T cells (9), other CD counts. If other CD count(s) routinely recorded, please give details.

(*continued*)

20. Which of the following post-procedure product (bag) information is routinely recorded (please select all that apply): white cell count (7), white cell differential (5), product CD34 count for PBSCs (13), product TNCs (9), product volume (20), product platelet count (5), product hematocrit (6), product CD3 count for lymphocytes for CAR T cells (7), other CD counts (0). If other CD count(s) routinely recorded, please give details.
21. Which of the following procedure information is routinely recorded: processed (21), CE1 (11), procedure (21), none of the above (0)
22. Do you routinely get a patient/donor cell count prior to the procedure (e.g., peripheral blood CD34 or total lymphocyte or mononuclear cell count): Yes (20), No (1). Please provide details.
23. Do you always receive a collection cell count following procedures: Yes (17), No (4). Please provide details.
    a. If yes, are you given a minimum/desirable/maximum bag yield before the collection (please select all that apply): minimum (11), desirable (6), maximum (3), none of the above (3)
    b. Is another collection required if a minimum bag yield is not achieved: Yes (11), No (0)
24. Do you monitor procedure CE (please select which CE is used, i.e., CE1/CE2). If not applicable, please select N/A
    a. PBSCs: CE1 (9), CE2 (6), N/A (6)
    b. DLI: CE1 (2), CE2 (2), N/A (17)
    c. Lymphocytes for immuno-oncology products: CE1 (0), CE2 (1), N/A (20)
    d. Mononuclear cellss for other ATMPs: CE1 (1), CE2 (0), N/A (20)
25. Is CVAD use/insertion routine for the collection of:
    a. PBSCs: Yes (4), No (16), N/A (1)
    b. DLI: Yes (1), No (14), N/A (6)
    c. Lymphocytes for immuno-oncology products: Yes (4), No (6), N/A (11)
    d. Mmononuclear cells for other ATMPs: Yes (1), No (7), N/A (13)
26. If CVAD use is routine (and thus insertion is elective), please select why this is routine: N/A (13), pediatric (5), to maintain flow/stable interface (5), lack of access to urgent CVAD insertion (2), need to ensure collection on specified date (3), other (1)
27. If peripheral access is routine, can urgent central access be arranged for:
    a. PBSCs: Yes (16), No (2), N/A (3)
    b. DLI: Yes (13), No (1), N/A (7)
    c. Lymphocytes for immuno-oncology products: Yes (7), No (3), N/A (11)
    d. Mononuclear cellss for other ATMPs: Yes (7), No (3), N/A (11)
28. Are labels for collection for CAR T cells and other ATMPs provided by the manufacturer or trial company: Yes (3), No (1), sometimes (5), N/A (12)
29. Do collections for CAR T cells and other ATMP products go directly to the manufacturer or trial company: Yes (4), No (3), sometimes (4), N/A (10)
30. Are transport boxes for cells collected for CAR T cells and other ATMP products provided by the manufacturer: Yes (7), No (2), sometimes (1), N/A (11)
31. If you collect cells for CAR T cells and other ATMP products, please provide details (if possible) of the products being collected and the trials being undertaken (trial/product name)
32. Does the ID and/or collection checking practice for collections of cells for CAR T cells and/or other ATMP products differ from your normal practice: Yes (2), No (9), N/A (10). If yes, please give further details.
33. Have you experienced any issues related to collections of cells for CAR T cells and/or other ATMP products related to any of the following: N/A (15), collection settings (3), labeling (4), packaging (2), training (4), documentation (2), other (0). Please give details.

AC, anticoagulant; CE, collection efficiency; DLI, donor lymphocyte infusion; ID, identity; N/A, not applicable; PBSCs, peripheral blood stem cells; SAMPLE, Standard Approach to ATMP Tissue Collection; TNCs, total nucleated cells.

contamination. Materials used in testing and procurement should be adequately stored and any temperature controls monitored.

The European Union (EU) Tissues and Cells Directive and UK Human Tissue (Quality and Safety for Human Application) Regulations refer specifically to testing requirements when collecting hematopoietic stem cells for transplantation. For autologous donors (i.e., patients), this includes mandatory infection marker testing within 30 days of collection and no requirement for testing immediately prior to collection (on the collection day). When a patient undergoes collection of a starting material for ATMP manufacturing, the UK Competent Authority does not permit omission of mandatory infection marker testing the day of collection, as the cells are not going to be used for hematopoietic stem cell transplantation; thus, mandatory infection marker testing the day of collection must be carried out on patients undergoing collection of starting material for ATMP manufacturing, and additional testing must be performed within 30 days of collection. Day of donation testing for allogeneic donors is mandated by the UK Competent Authority for hematopoietic stem cells and, by extension, for collection of the starting material for ATMP manufacturing.

The following tests must be performed: anti-HIV-1, anti-HIV-2, hepatitis B surface antigen, anti-hepatitis B core antibody, anti-hepatitis C virus antibody and *Treponema pallidum* serology. Anti-human T-lymphotropic virus type 1 antibody testing must be performed for high-risk patients, and the UK Government Advisory Committee on the Safety of Blood, Tissues and Organs [2,3] recommends that all allogeneic donors also be tested for hepatitis E virus, *Toxoplasma gondii*, Epstein–Barr virus and cytomegalovirus (CMV). The Advisory Committee on the Safety of Blood, Tissues and Organs also recommends HIV, hepatitis B virus, hepatitis C virus and hepatitis E virus nucleic acid testing and consideration of parvovirus B19. Epstein–Barr virus and CMV testing is largely for clinical information only; however, for some allogeneic ATMPs, particularly those in which the target patient population is immunosuppressed, CMV-negative allogeneic donors may be preferred.

Clinical Apheresis

All clinical apheresis units in the UK use the Spectra Optia device (Terumo BCT, Lakewood, CO, USA) for collecting MNCs.

Machine settings and procedure endpoints

The survey results showed a general consistency within a narrow range of machine settings and procedure endpoints. A total of 24 (83%) respondents indicated that machine settings were determined by their organization's policy, of which only eight (28%) specified that these were internally validated. A further eight (28%) revealed that settings were determined by the ATMP manufacturer's product or trial protocols. Machine settings should follow the apheresis system manufacturer's recommendations and must be validated in-house as part of the quality management system (QMS). The UK HTA and JACIE both require collection processes to be fully validated.

MNC/continuous MNC program

Software options for the Terumo BCT Spectra Optia device are the MNC and continuous MNC (CMNC) collection programs. Of the 29 clinical apheresis units, 22 (76%) used the MNC program only, six (21%) used both programs and one (3%) used only the CMNC program. Clinical apheresis units should procure starting ATMP materials using the program (MNC or CMNC) with which they are most familiar to optimize collection yields.

Starting flow rates for collection pumps used in CMNC varied between 1.0 mL/min and 1.2 mL/min. Nevertheless, all clinical apheresis units using CMNC may alter the flow rate to optimize collection. The apheresis system manufacturer's guidance should be followed if altering the default flow rates to meet requirements and optimize performance.

Anticoagulation

All clinical apheresis units used citrate-based anticoagulant citrate dextrose solution A (ACD-A) in compliance with the Spectra Optia certification. When setting collection parameters, consideration of hepatic function is necessary to allow for impaired citrate metabolism, particularly when body weight is low (especially in children). Calcium and magnesium are chelated by ACD-A during apheresis, so blood chemistry values should be assessed prior to each procedure to identify those who may need correction [4]. In children, the prophylactic use of calcium infusion should be carefully considered, as there is insufficient evidence to support this [5], although there is evidence highlighting the increased risk of citrate reactions in children [4,6].

Instead, early citrate toxicity detection measures, such as frequent monitoring of vital signs, should be undertaken, particularly in young children unable to verbalize. Common signs and symptoms of citrate toxicity include chills, abdominal pain, emesis, pallor, bradycardia and hypotension. However, if calcium replacement is required, there is no consensus regarding the route of calcium administration in children [5,7], as both intravenous and oral supplementation [8] are supported in the literature. If intravenous calcium replacement therapy is used during a collection in a small body weight child, intra-procedural ionized calcium monitoring should be considered on a case-by-case basis. The survey did not specifically ask what type of calcium supplementation was given. Anecdotally, the oral form of calcium replacement used in the UK is calcium carbonate and the intravenous form of replacement therapy used widely in the UK is calcium gluconate. Similarly, it was considered inappropriate to include dose and rate of calcium supplementation in the survey because the management of citrate toxicity is not specific to collection of starting material for ATMP manufacturing, and best practice would be for clinical practitioners to refer to local policy, published evidence and manufacturers' recommendations for these aspects of calcium administration to manage citrate toxicity.

Inlet:anticoagulant ratio

The survey found that most clinical apheresis units configure their devices to use an inlet:anticoagulant ratio of 12:1 for all procedures, although some were configured to a ratio of 13.5:1 and one reported using variable ratios for CAR T-cell collections. The apheresis system manufacturer's default inlet:anticoagulant ratio of 12:1 should be used to commence procedures, and inlet:anticoagulant ratio ramping should be switched on in MNC collections. Ratios may be changed to optimize collection or manage issues such as platelet aggregation. The range of inlet:anticoagulant ratios used should be within the apheresis system manufacturer's guidance range of 8:1 to 15:1, although exceptional circumstances can dictate the use of inlet:anticoagulant ratios outside this range. Since clinical apheresis units alter ratios during collection to manage procedural issues within the range specified by the apheresis system manufacturer, the stipulation of a specific inlet:anticoagulant ratio within an ATMP manufacturer's protocol would be redundant.

Anticoagulant infusion rate

Anticoagulant infusion rate settings ranged from 0.8 mL/min to 1.2 mL/min per liter of total blood volume (TBV), with most clinical apheresis units running at 1.1 mL/min per liter of TBV. None indicated that this setting was dependent on ATMP manufacturers' protocols for CAR T cells or other ATMPs. Most indicated that this setting was not routinely adjusted, but rather adjusted automatically with inlet flow changes. Some adjusted for low body weight and citrate toxicity symptoms.

These methods of use align with the apheresis system manufacturer's recommendations previously discussed, and any use of infusion rates outside of the specified range should be validated. Infusion rates above 1.2 mL/min must be used only in conjunction with calcium level monitoring and supplementation to prevent citrate toxicity. Special considerations will apply to small children with a TBV less than 1000 mL.

Procedure endpoints

The majority of clinical apheresis units used a multiple of TBV as an endpoint for procedures, often processing two to three TBVs, which in most cases provided adequate cell numbers for ATMP manufacturing [9]. However, in some circumstances (e.g., in autologous collections from heavily pre-treated patients or when higher cell yields are required), it may be necessary to process more than three TBVs, if feasible and safe to do so. Typically, the minimum expected cell collection requested is 2×10^6/kg, but this may differ in specific protocols, as is often the case in children and young people.

Some clinical apheresis units specified time as an endpoint, ranging from 3.1 h to 6.5 h. Time endpoints were used to achieve target cell yields in single collections for products transported directly to ATMP manufacturers. Most clinical apheresis units did not specify a minimum or maximum collection volume requirement, but a few reported requirements for certain products, such as CAR T-cell collections.

Overall, eight of 11 clinical apheresis units indicated that procedure endpoints were dependent on the ATMP manufacturer's protocol. To achieve a specified cell count, a predictive formula using pre-apheresis blood counts and the machine's collection efficiency can inform the number of TBVs to be processed, and this method of determining the TBVs to be processed may be preferred by some units.

Collection volumes should be calculated by the Spectra Optia based on validated machine settings, and any adjustments must comply with the apheresis system manufacturer's recommendations. Any reductions made to volumes processed or procedure times must not be detrimental to achieving the target cell yield.

Flush and chase volumes

In clinical apheresis units that used the MNC program, flush volumes of 16 mL were consistent in most, although chase volumes varied between 2 mL and 4 mL. There was greater variation among and within clinical apheresis units carrying out different procedures regarding final flush and chase volumes. The apheresis system manufacturer's recommendations for chamber flush and chase volumes (16 mL and 4 mL, respectively) should be followed to avoid reduced collection efficiency and increased cellular contamination with non-target cells.

Blood primes

The apheresis system manufacturer's recommendation in patients weighing less than 25 kg is to carry out a blood prime of the extracorporeal circuit. A weight of less than 25 kg corresponds to a TBV such that the extracorporeal circuit volume is greater than 10–15% of the TBV. When the extracorporeal circuit volume–TBV relationship is thus, use of a standard saline prime would result in significant hemodilution of the patient's circulation, which can be avoided by use of a blood prime. Charts of weights and their corresponding blood volumes can be drawn up locally to aid in the decision-making

Procedural Considerations

Patient, procedure and collection efficiency data

All clinical apheresis units should record a minimum set of data, including diagnosis, weight, height, peripheral blood leukocyte count, hematocrit, platelet count, TBV, volume processed, procedure time and target collection bag cell count (target yield). They should receive information on minimum target yield requirements, patient (or donor) pre-collection peripheral blood target cell thresholds and collection yields calculated by the ATMP manufacturer on receipt of the collection.

Clinical apheresis units should take samples from the collection bag sample bulbs to obtain in-house collection cell counts. This will act as a record of collection yield prior to distribution to the manufacturer and allow the machine collection efficiency to be calculated.

Central venous access devices and elective line insertion

Central venous access devices (CVADs) were routinely used in four clinical apheresis units performing CAR T-cell collections and in one clinical apheresis unit for other ATMP collections. Reasons given for

routine CVAD use in adults were (i) lack of access to urgent CVAD insertion services, (ii) to maintain a stable collection interface and (iii) to ensure collections could be carried out on specific pre-determined dates.

Experienced apheresis staff should perform a pre-collection peripheral vein assessment, and CVAD placement should be arranged prior to collection if deemed necessary. If time is critical (collection must be completed in a single day or the clinical apheresis unit does not have access to urgent line placement services), elective line insertion should be considered. Ultrasound-guided cannulation by experienced clinical apheresis unit staff may be considered in some centers as an alternative to CVAD insertion in selected patients.

Although peripheral access is possible in children, insertion of a temporary CVAD may be required in this age group to secure a steady flow rate that allows for uninterrupted and timely procedures. The need to successfully achieve cell collection in children should be balanced against line insertion risks [5,8]. However, these risks can be mitigated by femoral line placement with interventional radiology [6,10]. Optimization of inlet flow rates through adequate venous access improves collection efficiency and procedural time, with less citrate exposure and reduced hypocalcemia risk for children. Additionally, a constant but slower flow rate enables apheresis to occur efficiently, avoiding interruptions due to vasospasm and pressure alarms.

Processing and storage

In many cases, the fresh apheresis product is distributed to the ATMP manufacturer directly on completion of the procedure. Where temporary storage is required, this is usually at 4 ± 2°C in a monitored/alarmed blood refrigerator or within the validated conditions and equipment provided by the ATMP manufacturer. To reduce cellular stress, the total leukocyte concentration of the starting material should be below 200×10^9/L; this is a long-standing custom and practice in hematopoietic stem cell collection and cryopreservation facilities. Distribution or cryopreservation should occur within 48 h of collection and in accordance with the ATMP manufacturer's requirements.

Cryopreservation and thawing

Although it comes with possible drawbacks regarding the longer overall manufacturing process, cryopreservation allows longer-term storage of the starting material and can assist in managing logistics and scheduling flexibility. Cryopreservation can be used either in the health care system or within the manufacturer to create flexibility. Several steps and factors should be considered: cryoprotectant addition and concentration, protein source, passive or controlled-rate freeze, validation of a controlled freeze rate program, validation if the sample volume/container/cryobag size is varied, cryostorage temperature limits and high alarm triggers. Thawing procedures are also critical to cellular integrity [11]. Post-thaw viability assays should be part of the validation of cryopreserved starting materials.

The cryogenic shipper and storage units should be qualified and validated. The quality assurance of the processing laboratory must confirm that the starting material has met pre-determined release criteria and export licensing requirements if applicable.

Labeling and Traceability

All procurement of tissues and cells for human use in the UK must occur under appropriate licensure (HTA) consistent with a unique legal identifier on the label or accompanying the product.

Starting material labeling and documentation

Starting material collection processes, including paperwork, identity checking and pre-collection labeling of product bag requirements, vary across collection and processing facilities. All facilities reported having documentation and identity checking processes consistent with accreditation requirements and as requested by CAR T-cell and other ATMP manufacturers. Facilities performing MNC collections for CAR T-cell and other ATMP manufacturers indicated that labels are sometimes supplied by the ATMP manufacturer, although not all labels are compliant with HTA and JACIE requirements.

Initial labeling of starting material

Starting material labeling must allow traceability. All UK and EU apheresis facilities involved in cell collection for ATMP manufacturing must use labels that meet regulatory and JACIE requirements and follow the internationally recognized ISBT 128 standards. The donation identification number (DIN) and Single European Code (SEC) [12] ensure that donations are unique and traceable and are a requirement for procurement in Northern Ireland and the EU but are no longer required in Great Britain.

ISBT 128 and international consistency

ISBT 128 is the international information standard for medical products of human origin. This labeling system enables identification and information exchange regarding biological products using standard terminology between digital systems while ensuring traceability throughout collection, processing, transport, manufacturing and final product. It has gained international acceptance and is now in widespread use. ISBT 128 cell therapy product labels (standard ST-018, ISBT 128 Standard Labeling of Collection Products for Cellular Therapy Manufacturing v1.0.0) [13] contain a unique DIN consisting of 13 characters that represent the country and clinical apheresis unit that assigned the DIN, donation year and unique sequence number. Clinical apheresis unit codes are assigned by the International Council for Commonality in Blood Banking Automation [14]. In addition, product codes are constructed by international consensus to ensure global consistency and understanding. Cellular product terminology and coding are managed by the International Council for Commonality in Blood Banking Automation and the International Cellular Therapy Coding and Labeling Advisory Group. Together, the DIN and product code identify a specific product bag, including starting material and intermediates.

Single European Code

The SEC is a unique identifier used within the EU and Northern Ireland. It consists of two parts: the donation identification sequence, or SEC-DI, which indicates the origin of the cells, and the product identification sequence, or SEC-PI, which classifies the type of cells. Where cells are transferred to another organization for further processing or ATMP manufacturing, at a minimum, the SEC-DI must accompany the cells, at least in the accompanying documentation if not on the collection label. The SEC-DI comprises the country of origin code, Tissue Establishment (clinical apheresis unit) number and unique donation number (ISBT 128 DIN). Although no longer required in Great Britain, it is necessary for materials collected in Northern Ireland and the EU. Thus, if an apheresis collection requires distribution to an ATMP manufacturer based in the EU or Northern Ireland, a SEC-DI will need to be applied either at the point of procurement or at the point of import into the EU or Northern Ireland.

Labeling collections to meet ATMP manufacturer requirements

Currently, the labeling required by clinical trial sponsors and ATMP manufacturers is variable. ATMP manufacturers' labeling policies are heterogeneous; some allow a clinical apheresis unit's existing procurement labels, whereas others ask for DIN and SEC, request

extra data or provide pre-printed labels. As these may not meet regulatory requirements, regulatory-compliant labeling should be added. Personally identifiable information should not be included in the label unless justified. Standard hand-held bar code readers can be used to ensure that the relevant barcoded data on the patient's wristband are also present on the collection bag label applied to the bag base label, but this should be considered an additional safety step and not an alternative to a two-person check of the relevant data on the collection bag label against the patient's data (either directly with the patient or from hard copy documentation). Sticking a label on the collection bag directly and not on the base label is not recommended because this may interfere with the bag's gas permeability. If the obscuring of patient identifiable data is required, sticking the manufacturer's supplied label on top of the "local" collection label (that has been applied to the bag base label) at the end of the collection is an option so long as the manufacturer's label meets all regulatory and accreditation requirements.

Quality management, audit and regulatory compliance

The collection of starting material for ATMP manufacturing is regulated under frameworks covering the procurement of tissues and cells for direct human use. In the UK, collection is regulated under the Human Tissue (Quality and Safety for Human Application) Regulations 2007 [15] and Human Tissue Act 2004 (England and Wales) [16] as well as Human Tissue Act (Scotland) 2006 [17], and in the EU and Northern Ireland, it is regulated under the EU Tissues and Cells Directive (2004/23/EC) [18] and associated Commission Directives [12,18]. Accreditation body standards, such as the Foundation for Accreditation of Cellular Therapy (FACT)–JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, also help ensure that collections occur in a controlled and safe environment [19].

Quality management

The implementation of a QMS allows collection and processing facilities to satisfy multiple regulatory and accreditation requirements depending partly on whether the clinical apheresis unit is within a hospital or a blood service. The QMS should meet the HTA standards for Governance and Quality.

Quality technical agreement

The manufacturer's QMS requires qualification of the supplier to determine their suitability and eligibility to procure the starting material on their behalf. Eligibility is based on the scope of the clinical apheresis unit's license and the procurement and testing activities it will undertake. Once the assessment has been completed, written agreements defining the relationships and responsibilities of the parties can be produced. Collection facilities have a regulatory responsibility to execute quality technical agreements (QTAs) with other facilities and ATMP manufacturers to define the respective responsibilities, ensure that licensing and accreditation obligations are met and avoid confusion regarding responsibilities. The required specifications of apheresis collections should be defined in a mutually agreed quality technical specification (QTS). The content of these documents (QTA and QTS) should be in accordance with the HTA Guide to Quality and Safety Assurance for Tissues and Cells for Patient Treatment 2021 and UK Orange (Good Manufacturing Practice [GMP]) guide or, in the EU, EudraLex Volume IV GMP guidelines (Part IV GMP, Section 13: Outsourced activities) [20].

Serious adverse events and reactions

The QTA should define reporting responsibilities for any donation-associated serious adverse event or reaction. The ATMP manufacturer should be responsible for reporting incidents during transport that may impact on quality or safety and any cell defect that may indicate that an error occurred during procurement, storage, transfer or processing. The HTA license holder remains responsible for collection-related serious adverse event/reaction notifications to the HTA. Feedback on the quality of cells is a JACIE requirement, and collection facilities may ask ATMP manufacturers to provide information on the outcome of tests undertaken on the starting material.

Changes to export/import licenses for Great Britain, Northern Ireland and the EU

Now that the UK has exited the EU, an HTA import license is needed to import starting material into Great Britain from the EU or to export it from Great Britain to the EU/Northern Ireland (mandatory beginning July 1, 2021). Beginning January 1, 2021, facilities in Northern Ireland are required to treat Great Britain suppliers according to the relevant EU regulations for non-EU suppliers and will need an import license. Neither body requires additional licenses to export/import material from Northern Ireland to Great Britain.

Although import and export customs requirements may vary, all member states require an Economic Operators Registration Identification (EORI) number to/from the relevant EU authority. Shipments from the UK to EU will require an EU EORI, and the reverse will require a Great Britain EORI. The UK Government customs declaration requirements for substances of human origin used in grafting, implanting or transfusion for imports and exports under the Border Operating Model is a useful reference point [21]. Different government agencies may also have requirements or restrictions for shipping cellular material. Therefore, such requirements must be clearly understood prior to shipment, as permits may take time to obtain.

Discussion

The quality and safety of ATMPs are dependent on the provenance of the supply and are significantly impacted by variation in the starting material. Although biological variation is, to some extent, unavoidable, procedural variation may be mitigated by standardization. Variation in working practices among different clinical apheresis units and in requirements among different ATMP manufacturers causes problems for both parties and results in duplication, inefficiency and increased risk of non-compliance. This problem is likely to worsen over the coming years, as an increasing range and larger number of starting materials are required to support pivotal trials and more widespread clinical adoption of ATMPs.

A review of the procurement of starting materials by apheresis for ATMP manufacturing was initiated as part of the UK Advanced Therapy Treatment Centre Network Standard Approach to ATMP Tissue Collection project (https://www.theattcnetwork.co.uk/). The objective was to bring together stakeholders from across the academic, commercial and health care ATMP communities to agree on standardized approaches to MNC procurement. A survey was sent out to 36 UK clinical apheresis units, with a return rate of 80% (29 clinical apheresis units), which included most of the major units and approximately 70% of the annual MNC collections in the UK.

Donor screening tends to be standardized across units in compliance with the requirements of the HTA [15] and the UK Government's Advisory Committee on the Safety of Blood, Tissues and Organs [2]. All clinical apheresis units in the UK use the Terumo BCT Spectra Optia device for collecting MNCs. The survey results revealed a general consistency within a narrow range of machine settings and procedure endpoints; however, there was variation in the extent to which these were determined by the organization's policy or the ATMP manufacturer's product or trial protocols, and only a minority of clinical apheresis units specified that these were internally validated. Machine settings should follow the apheresis system

manufacturer's recommendations and must be validated in-house as part of the QMS. Clinical apheresis units should procure starting ATMP materials using the software program (MNC or CMNC) with which they are most familiar to optimize collection yields. Citrate-based ACD-A is the anticoagulant of choice, and the apheresis system manufacturer's default inlet:anticoagulant ratio of 12:1 should be used to commence procedures. Ratios may be changed to optimize collection or manage issues such as platelet aggregation but should remain within the apheresis system manufacturer's guidance range of 8:1 to 15:1. Anticoagulant infusion rate settings ranged from 0.8 mL/min to 1.2 mL/min per liter of TBV, with most clinical apheresis units running anticoagulant rates of 1.1 mL/min per liter of TBV, adjusted automatically with inlet flow changes. Most clinical apheresis units use TBV as a procedure endpoint, though some use time. Collection volumes should be calculated by the Spectra Optia based on validated machine settings, and any adjustments should comply with the apheresis system manufacturer's recommendations. Any reductions made to volumes processed or procedure times must not be detrimental to achieving the target cell yield. The apheresis system manufacturer's recommendations for chamber flush and chase volumes (16 mL and 4 mL, respectively) should be followed to avoid reduced collection efficiency and increased cellular contamination with non-target cells.

It is recommended that all clinical apheresis units record a minimum set of data, including diagnosis, weight, height, peripheral blood leukocyte count, hematocrit, platelet count, TBV, volume processed, procedure time and target collection bag cell count (target yield). They should receive information on minimum target yield requirements, patient (or donor) pre-collection peripheral blood target cell thresholds and collection yields calculated by the ATMP manufacturer on receipt of the collection. Clinical apheresis units should take samples from the collection bag sample bulbs to obtain in-house collection cell counts, which act as a record of collection yield prior to distribution to the ATMP manufacturer and allow the machine collection efficiency to be calculated.

In most cases, the fresh apheresis product is distributed to the ATMP manufacturer directly on completion of the procedure; however, where temporary storage is required, this is usually at 4 ± 2°C in a monitored/alarmed blood refrigerator or within the validated conditions and equipment provided by the ATMP manufacturer. To reduce cellular stress, the total leukocyte concentration of the starting material should be below 200×10^9/L, and distribution or cryopreservation should occur within 48 h of collection and in accordance with the ATMP manufacturer's requirements. Some ATMP manufacturers require local cryopreservation of the starting material. Where this is the case, several steps in the freezing, storage, shipping and thawing processes need to be validated. Post-thaw viability assays should be part of the validation of cryopreserved starting materials.

Starting material collection labeling practices vary across collection and processing facilities and sometimes between different ATMP manufacturers. All UK and EU apheresis facilities involved in cell collection for ATMP manufacturing must use labels that meet regulatory and FACT-JACIE [19] requirements and follow the internationally recognized ISBT 128 standards. The DIN and SEC [12] ensure that donations are unique and traceable and are a requirement for procurement in Northern Ireland and the EU; however, following its exit from the EU, they are no longer required in Great Britain, where ISBT 128 cell therapy product labels (standard ST-018, ISBT 128 Standard Labeling of Collection Products for Cellular Therapy Manufacturing v1.0.0) [13] are a suitable alternative. The SEC is still required for export of starting material for ATMP manufacturing from Great Britain to Northern Ireland or the EU. Some ATMP manufacturers request use of their own labels, but if these are not compliant with regulatory requirements, both labels may be required. Personally identifiable information should not be included in the label unless justified.

The collection of starting material for ATMP manufacturing is regulated under UK and EU legal frameworks covering the procurement of tissues and cells for direct human use and FACT-JACIE international accreditation standards [19] and should be managed under the aegis of an organizational QMS. Collection facilities have a regulatory responsibility to execute QTAs with other ATMP manufacturers to define the respective responsibilities, and the required specifications of apheresis collections should be defined in a mutually agreed QTS.

Finally, now that the UK has exited the EU, an HTA import license is needed to import starting material into Great Britain from the EU or to export from Great Britain to the EU and Northern Ireland (mandatory beginning July 1, 2021). Beginning January 1, 2021, facilities in Northern Ireland are required to treat Great Britain suppliers according to the relevant EU regulations for non-EU suppliers and will need an import license. Neither body requires additional licenses to export/import material from Northern Ireland to Great Britain. The main recommendations are summarized in Table 2.

Table 2
Recommendations.

1	Machine settings should follow the apheresis system manufacturer's recommendations and must be validated in-house as part of the QMS.
2	Clinical apheresis units should procure starting ATMP materials using the software program (MNC or CMNC) with which they are most familiar to optimize collection yields.
3	The apheresis system manufacturer's default inlet:AC ratio of 12:1 should be used to commence procedures.
4	Inlet:AC ratios should remain within the apheresis system manufacturer's guidance range of 8:1 to 15:1.
5	Collection volumes should be calculated by the Spectra Optia based on validated machine settings, and any adjustments should comply with the apheresis system manufacturer's recommendations.
6	Any reductions made to volumes processed or procedure times must not be detrimental to achieving the target cell yield.
7	The apheresis system manufacturer's recommendations for chamber flush and chase volumes (16 mL and 4 mL, respectively) should be followed to avoid reduced collection efficiency and increased cellular contamination with non-target cells.
8	Clinical apheresis units should record a minimum set of data, including diagnosis, weight, height, peripheral blood leukocyte count, hematocrit, platelet count, TBV, volume processed, procedure time and target collection bag cell count (target yield).
9	Clinical apheresis units should receive information on minimum target yield requirements, patient (or donor) pre-collection peripheral blood target cell thresholds and collection yields calculated by the ATMP manufacturer on receipt of the collection.
10	Clinical apheresis units should take samples from the collection bag sample bulbs to obtain in-house collection cell counts, which act as a record of collection yield prior to distribution to the ATMP manufacturer and allow the machine collection efficiency to be calculated.
11	To reduce cellular stress, the total leukocyte concentration of the starting material should be below 200×10^9/L, and distribution or cryopreservation should occur within 48 h of collection and in accordance with the ATMP manufacturer's requirements.
12	Where local cryopreservation is required, several steps in the freezing, storage, shipping and thawing processes need to be validated.
13	Post-thaw viability assays should be part of the validation of cryopreserved starting materials.
14	All UK and EU apheresis facilities involved in cell collection for ATMP manufacturing must use labels that meet regulatory and FACT-JACIE requirements and follow the internationally recognized ISBT 128 standards.
15	Personally identifiable information should not be included in the label unless justified.
16	The collection of starting material for ATMP manufacturing should be managed under the aegis of an organizational QMS.
17	Collection facilities have a regulatory responsibility to execute QTAs with other ATMP manufacturers to define the respective responsibilities, and the required specifications of apheresis collections should be defined in a mutually agreed QTS.

AC, anticoagulant.

Conclusions

ATMPs must be procured and manufactured according to standards that ensure the highest levels of safety and quality before administering the product to a patient. Because of the multiple collection facilities and manufacturers involved in the procurement of starting materials, the risk of inefficiency and non-compliance increases as the range and volume of starting materials needed to support pivotal trials and clinical adoption of ATMPs increase. To mitigate this, the authors have attempted to develop a set of consensus guidelines around donor selection and screening, clinical apheresis procurement, storage, labeling and traceability. The processes at each stage of the ATMP supply chain must be controlled and standardized wherever possible to ensure quality and safety, improve process efficiency and reduce the risk of error while meeting all regulatory and accreditation requirements. The authors regard the current work as a starting point for further discussion on an international level and recognize that further refinement and evolution are inevitable as ATMPs move into routine clinical practice.

Declaration of Competing Interest

JS is an employee of and has stock ownership in bluebird bio, Inc. DH was employed by Autolus Therapeutics plc during the drafting of the manuscript. WS is employed by Autolus Therapeutics plc.

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Author Contributions

Conception and design of the study: . Acquisition of data: . Analysis and interpretation of data: . Drafting or revising the manuscript: . All authors have approved the final article. All the authors contributed to all aspects of the work through the steering group.

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Supplementary materials

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