Advanced Therapy Treatment Centres

UK REVIEW AND RECOMMENDATIONS ON THE PROCUREMENT OF STARTING MATERIALS BY APHERESIS FOR ADVANCED THERAPY MEDICINAL PRODUCT (ATMP) MANUFACTURE

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1. Introduction

Advanced Therapy Medicinal Products (ATMPs) must be safe and of high quality when administered to a patient. To achieve these aims, the activities carried out at each stage of the ATMP supply chain must be controlled and standardised wherever possible to ensure the quality and safety of the medicinal product, improve the efficiency of the process, and reduce the risk of error while meeting all regulatory and accreditation requirements.

This process of control and standardisation is particularly challenging in the context of cellular, gene-modified cellular, and tissue-engineered therapies where the starting material is procured from a patient or healthy donor in the healthcare environment. Many ATMPs are manufactured from peripheral blood mononuclear cells (PBMCs), (e.g. T cells, natural killer (NK) cells, monocytes, haematopoietic stem and progenitor cells), procured using clinical apheresis.

There are around 50-60 clinical apheresis units (CAUs) across the UK involved in MNC procurement mainly for haematopoietic stem cell (HSC) transplantation, and these operate under the aegis of a Human Tissue Authority (HTA) licensed establishment[1] and Joint Accreditation Committee ISCT / EBMT (JACIE) accreditation. However, variation exists in working practices between different CAUs which is problematic for manufacturers needing to control the quality of their starting materials (so far as is possible) through standardised processes. By the same token, there is variation between different manufacturers' requirements posing challenges for individual CAUs who find it difficult to manage multiple different protocols for the same starting material leading to duplication, inefficiency and increased risk of non-compliance for both sets of stakeholders. This systematic problem is likely to worsen over the coming years as an increasing range and volume of starting materials are required to support pivotal trials and clinical adoption of ATMPs.

[1]In the UK, ATMP starting material procurement by apheresis can be made under the Human Tissue Authority (HTA) Tissue Establishment or Medicines and Healthcare products Regulatory Agency (MHRA) Blood Establishment licensure. In clinical settings collection is normally made under HTA licence in accordance with Human Tissue (Quality and Safety for Human Application) Regulations.

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This review was initiated as part of the UK Advanced Therapy Treatment Centre Network SAMPLE project (https://www.theattcnetwork.co.uk/) with the objective of bringing together stakeholders from across the academic, commercial and healthcare ATMP community to work together to agree standardised approaches to mononuclear cell procurement to reduce unnecessary complexity and variation.

Questionnaires were sent out to a number of manufacturers, collection facilities and processing facilities in the UK, to understand the current range of practice in clinical apheresis collection (Sections 4, 5, and Appendix A), processing and storage (Section 6), labelling and traceability (Section 7). Reviews were also carried out of transport logistics (Section 8), quality management, audit and regulatory compliance (Section 9).

2. Note on Nomenclature

Nomenclature is complex in this area because of the involvement of organisations from different sectors in the field and extrapolation from a range of existing accreditation and regulatory frameworks which were primarily designed for other purposes leading to the use of similar terminology for different things. For the purposes of this document nomenclature is used in the following way:

ATMP: Advanced Therapy Medicinal Product as defined in EC Regulation 1394/2007. These may be Licensed, for use in Clinical Trial or released under Specials or Hospital Exemption.

Donors: may be autologous (patients), related allogeneic (e.g. family members) or unrelated allogeneic.

Collection facilities: refers to Clinical Apheresis Units in the healthcare system.

Processing facilities: refers to separate storage and cryopreservation facilities within the healthcare system. They may be within the same organisation and HTA licensure as the collection facility or in a different organisation.

ATMP manufacturers: refers generically to any manufacturer of the ATMP whether commercial or within a non-commercial setting (e.g. an academic or healthcare organisation)

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and irrespective of whether in the same or a different organisation as the collection and processing facilities.

Mononuclear cells (MNC): refers to the product procured by apheresis which forms the starting material for the manufacture of the ATMP.

Haematopoietic stem and progenitor cells (HSPC): are a subset of the CD34+ population of MNC.

T lymphocytes: are a subset of the MNC population usually identified through CD3 expression.

The terms cellular therapies, cellular therapy products and somatic cell therapies are used variously to (appropriately) describe the direct use of HSPC in transplantation and the manufactured medicinal products. Because of this ambiguity, these terms are avoided in this document and the terms *MNC*, *starting materials* and *ATMPs* used instead as appropriate.

Quality Technical Agreement: is the term used to describe the agreement between parties that sets out the quality and regulatory requirements and the roles and responsibilities of the various parties.

Quality Technical Specification: is the term used to describe the specification of the starting material agreed by the ATMP manufacturer with the collection facility (and, where appropriate, the processing facility).

3. Overview of Process Flow

An overview of process flow was developed in order to structure a more detailed analysis of key steps in the process.

Donor-related factors have the potential to impact on the quality of the cellular collection. As the starting material may originate from healthy donors or patients, biological variability between and within donors may affect the quality of the cells collected. Patient-related factors of relevance will include underlying diagnosis, prior and current treatment and current health. Also, interaction with ATMP manufacturers whose processes are managed

within different regulatory frameworks to those of the collection and processing facilities may result in an unwarranted change to the standard processes through lack of understanding of acceptable similarities and differences between organisational regulatory and accreditation requirements.

There is limited capability to control donor-related factors that could impact on the quality of cell collections, and so the focus has to be on control and standardisation of the collection process and collaborative working with ATMP manufacturers to promote a mutual understanding of processes.

Regulatory frameworks are already in place that underpin cell collection process control. The collection of starting material for ATMP manufacture is regulated under the frameworks covering the procurement of tissues and cells for direct human use; in the UK this is performed under the Human Tissue (Quality and Safety for Human Application) Regulations 2007,[1] as amended, or in the European Union (EU) under the Tissues and Cells Directives (2004/23/EC) as transposed into Member State law. Accreditation bodies' standards such as the Foundation for Accreditation of Cellular Therapy (FACT) – Joint Accreditation Committee ISCT Europe and EBMT (JACIE) International Standards for Haematopoietic Cellular Therapy Product Collection also play a role within the collection facilities in ensuring collections are carried out in a controlled and safe environment.

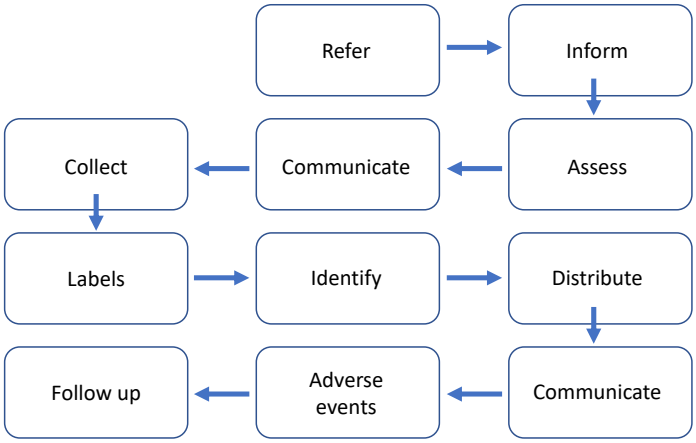
An exemplar process flow for the apheresis collection of ATMP starting material is described (Diagram 1), areas of challenge and uncertainty are highlighted and possible solutions suggested. The foundation for collection process control should be the FACT-JACIE collection standards as apheresis collection of MNC for ATMP manufacture both of licensed products and those within the context of a clinical trial fall within the scope of this accreditation framework, in addition to other useful immune effector cell (IEC) standards.[2] JACIE states that compliance with its standards does not guarantee compliance with all applicable laws and regulations – governmental regulations must also be followed and the individual collection facility is responsible for determining which laws and regulations are applicable. In some cases, regulations of governmental authorities outside the jurisdiction within which the facility operates may apply; for example, when a facility sends starting materials to another country. Compliance with other organisations' standards or governmental regulations does

not ensure that the JACIE standards have been met. JACIE's position is that governmental regulations supersede its standards if those regulations set a higher standard or are inconsistent with a specific JACIE standard. However, if a JACIE standard is more rigorous than a governmental regulation, that standard must be followed.

The regulatory, accreditation and guidelines frameworks of relevance to the apheresis collection of ATMP starting material are set out (Table 1).

Collections can be carried out as part of the donor's standard management plan (the patient), within a clinical trial (the patient, the related or the unrelated allogeneic donor) or as an elective donation (the unrelated donor). The term 'donor' is used even in the autologous setting because considerations for informed consent and suitability (i.e. safety) of the individual include issues above and beyond the individual's status as a patient receiving a cellular therapy. If there are additional requirements specific for a particular subgroup, the detail and applicability of these requirements will be made explicit.

Diagram 1. Exemplar Process Flow: Apheresis collection of ATMP starting material.



Explanatory Notes

Refer *donor from the clinical or donor team to the collection facility*: there must be a clinician who is responsible for the welfare and wellbeing of the donor. For the patient, this is usually their clinician, and for the related allogeneic donor, a member of the clinical team who is not

directly responsible for their sibling. For the unrelated donor, this is likely to be a member of the donor team. There must be a written order from the referring team detailing the specific requirements of the collection. This should include (but not be limited to) detail on the planned day of collection, acceptable laboratory parameters for the donor's vital organ function before and after the collection, the type of cell to be collected, and the target collection yield. Where the target collection yield is not known, the total blood volume to be processed should be given. The donor unique identifier, clinical trial name, and the donor's trial identifiers should be given, as indicated.

Inform, *counsel and consent the donor on the collection process*: these activities may be done by the referring team before referral of the donor for collection is made, or by the collection facility team after referral. Process control is required irrespective of who is undertaking these activities. An information leaflet describing the collection process, its side effects and their treatments and alternatives to undergoing collection can be used to augment the face-to-face information transfer. The information leaflet can be given to the donor in advance of the face-to-face assessment, and any questions arising from the leaflet content or during the face-to-face assessment discussed. The information leaflet must be age-appropriate, written wherever possible in the first language of the donor, and use language and terminology that can be understood by the donor. If there are communication challenges, these must be overcome to ensure that the donor is fully informed about the collection process: the support of an interpreter or play leader may be required, and large print leaflets for those with visual challenges may be helpful. The consent process, including the use of written and verbal information, must be Montgomery compliant. The specific needs of a donor with incapacity who has been referred for collection must be met.

Assess *the suitability of the donor to undergo the collection process*: assessment activities may be done by the referring team according to the Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) donor selection guidelines,[3] and the Geographical Disease Risk Index (GDRI)[4] as a resource for assessing allogeneic donors, before referral of the donor for collection is made or by the collection facility team after referral. Process control is required irrespective of who is undertaking these activities. Suitability includes ensuring that the donor's health and wellbeing are not compromised by undergoing the collection process. The donor's eligibility

to donate must also be determined to ensure that the risk of infection or other disease transmissions through procurement, storage, manufacture and administration is minimised and that by so doing, all regulatory requirements relating to infection or other disease transmission are met. In patients, the donor of the starting material is also the recipient of the medicinal product and so the risk of transmission of certain infectious, immune or neoplastic diseases may not apply, although should be considered based on the manufacturing process and product type. However, the patient must still not be exposed to any undue risk by undergoing collection and the quality and safety of the starting material must not be compromised by, for example, contamination from an ongoing bacterial infection. If there is doubt as to the medical suitability of the donor, local donor acceptance criteria can be consulted and a specialist opinion sought. In the case of allogeneic donation, the donor would be expected to test negative for all applicable mandatory adventitious agent testing, which varies from country to country so a comprehensive approach is recommended to maximise the utility of the donation.

When collecting from an autologous donor there may also be a limited window of opportunity to undertake the collection when the patient's performance status is adequate following previous treatments and before progressive disease takes over. A careful risk-benefit assessment of the suitability of the patient should be carried out on a case-by-case basis. Care must also be taken to protect the staff and facilities involved in collection and manufacturing, and to ensure that the risk of cross-contamination of any other products manufactured in the same facility is minimised by testing the patient for the standard mandatory markers of infection (hepatitis B, hepatitis C, HIV, HTLV and syphilis). For ATMP this should be done on the day of collection. For GMP reasons the donor may also be tested prior to the day of collection. The need and timing of testing before the day of collection will depend on product type (autologous/allogeneic) and should be risk based and should be within 30 days prior to collection.

When collecting from an allogeneic donor, the suitability of the donor must be assessed as well as their eligibility to donate as aspects of their health may impact on the quality and safety of a manufactured medicinal product that could be used to treat numerous patients over several years. Allogeneic donors must undergo a full medical, travel, social and

behavioural history as well as a physical examination and baseline organ function and mandatory infection marker testing.

Allogeneic donor travel (both recent and in the distant past) needs to be considered when assessing the risk of travel-related infections that may be transmitted through the donated material. An assessment of the potential allogeneic donor's social and behavioural risks must be carried out due to the risk of infectious window period donations. Evidence of high-risk behaviour in the allogeneic donor (such as tattoos in a non-regulated environment or intravenous drug use) should lead to donor deferral even in the face of negative results for markers of currently identified infections.

If a potential related allogeneic donor does not meet screening criteria but there is an urgent clinical need such that deferral of the donor would result in greater risk to the intended recipient than the use of the ineligible donor, a documented protocol exception can be considered subject to a risk assessment on a case-by-case basis and the agreeance of the approved Designated Individual for the collection facility.

Communicate *assessment findings and eligibility to donate to the collection facility (if assessment carried out by the clinical or donor team before referral), the ATMP manufacturer, the referring team (if assessment carried out by the collection facility) and the family doctor*: there must be written confirmation that the donor is suitable and eligible to undergo collection. The extent of information that relates to the donor's suitability and eligibility to undergo collection that has to be shared with the ATMP manufacturer must be determined in advance of the collection. The information must be captured in a written agreement between the collection facility and the ATMP manufacturer and information sharing carried out in a way that is consistent with mandated data protection requirements.

Donor undergoes ***collection*****:** the donor must undergo an immediate pre-collection health check to ensure his/her circumstances have not changed significantly since the pre-collection assessment and that s/he is fit to undergo collection, and the findings must be recorded. The collection is carried out according to either the collection facility's standard collection protocol or to the ATMP manufacturer's apheresis protocol. The collection facility should

review the ATMP manufacturer's protocol and document variances against the standard collection protocol in an aide-mémoire format to reduce the likelihood of errors being made in the collection process. The extent of information that relates to the donor's suitability and eligibility to undergo collection that has to be shared with the ATMP manufacturer must be determined in advance of the collection. Staff must be trained against the aide-mémoire document to ensure that each ATMP manufacturer's collection requirements are met.

In the UK, apheresis used as ATMP starting material can be procured under the Human Tissue Authority (HTA) Tissue Establishment or Medicines and Healthcare products Regulatory Agency (MHRA) Blood Establishment licensure. The preference within a clinical setting is to collect under an HTA licence which is consistent with Human Tissue (Quality and Safety for Human Application Regulation 2007, as amended requirements.

For autologous donors this should include mandatory infection marker testing prior to and on the day of collection. If required, the timing of the mandatory testing prior to the day of collection should be justified.

Results of the day of collection mandatory infection marker testing are to be shared with the ATMP manufacturer. This must be captured in a written agreement, and information sharing carried out in a way which is consistent with mandated data protection requirements. As day of donation test results will not be available until after the collection bag has left the control of the collection facility, warning and biohazard labels must be placed on the collection bag if there are positive test results, incomplete testing or unavailability of results from the pre-collection assessment testing. The ATMP manufacturer should be informed of the need to use these labels, and the requirement that if used, the collection bag is handled in such a way that is consistent with legislated data protection requirements.

*Product and warning **labels** must be applied to the collection bag to allow donor and product identification*: donor-identifiable data must be placed on the collection bag label and it is advised that the accuracy of the data is verified before the procedure starts and again before

the bag is removed from the immediate vicinity to ensure that the cells in the bag have originated from the donor named on the bag. The MHRA have advised this identifiable labelling should be suitably anonymised to ensure the donor is not identifiable to all non-collection staff. The quality procedures in place at the collection facility should ensure accurate identification and traceability of the donor and all donations.

Great Britain (GB) is no longer mandated to follow Eurocode standard terminology, and include the alphanumeric identifier consistent with the Single European Code legislation (SEC-donor identification sequence), and it will no longer be possible to request EU codes for new centres and products. Northern Ireland (NI) and the EU countries will continue to use these.

A new global recommendation for the labelling of apheresis collections for use in the manufacture of ATMP has been released by ICCBAA; ISBT 128 STANDARD Labeling of Collection Products for Cellular Therapy Manufacturing ICCBBA ST-018.[5] It is recommended that centres work to adopt this global standard label as soon as possible.

When used, all hand-written data must be written in indelible ink that will not smudge during distribution and on receipt by the ATMP manufacturer.

*As a minimum, a unique **identifier** must remain on the cellular therapy product label at the point of distribution to the ATMP manufacturer. The MHRA strongly recommend patient identifiable data are redacted prior to distribution*: the general principle of the data protection regulations in the UK is to minimise sharing of data collected, and share any data used on a need-to-know basis only. It follows that if an individual does not need the data to carry out his/her activity, s/he should not have access to it. Therefore, sharing of all personally identifiable information (PII) should be minimised as much as is practically reasonable. Once data are outside the collection facility's control, it may be used by the ATMP manufacturer; this carries a legal and reputational risk for the collection facility if data are shared with individuals within the ATMP manufacturer who do not need access.

The ATMP manufacturer and the collection facility must decide in advance of the collection bag leaving the control of the collection facility the extent of Personal Identifiable Information (PII) which remains visible on the collection bag label and accompanying documentation, and all unnecessary data must be erased. A unique identifier containing no PII must be applied to the collection bag and accompanying documentation as a minimum before distribution if all other PII has been erased. If the donor's starting material has been collected as part of a clinical trial, this may be the unique participant study number. A process must be in place whereby the unique identifier can be associated with the donor and the donation from the point of distribution from the collection facility through all steps of manufacturing to reinfusion into the patient. If PII is to be used, then this needs to fully justified and discussed with the appropriate body.

The starting material leaves the control of the collection facility and is distributed: the collection bag may be distributed to the local processing facility or direct to the ATMP manufacturer. Once at the local processing facility, it may be processed prior to onward distribution to the ATMP manufacturer, or remain for local manufacture. Validated distribution boxes must be used and it must be agreed in advance between the collection facility, the processing facility and the ATMP manufacturer who is responsible for box validation and supply as well as the means by which the product will be distributed (e.g. by in-house driver or by external courier).

The roles and responsibilities of each party in the starting material distribution process must be explicitly set out between the collection facility, the processing facility, and the ATMP manufacturer; the service level must be clearly defined and responsibility for audit of the distribution process to ensure the agreed service level is met will lie with the ATMP manufacturer. The roles and responsibilities may be defined within a Quality Technical Agreement if the processing or manufacturing activities are undertaken by external organisations, or within a policy document within the organisation's quality management system if carried out internally.

Storage within the collection facility is normally defined as from the end of the collection procedure until the starting material leaves the control of the collection facility, however responsibility for storage should be clearly set out in the Quality Technical Agreement. Short

term storage (≤48h) coincident with uplift and transport to the manufacturer is permissible without the need of an HTA storage licence. Short- and longer-term storage conditions must be defined and actions to take if storage conditions fall outside of the specification determined.

There must be documentation of the starting material leaving the control of the collection facility and being handed over to the control of the courier (for onward distribution to the processing facility or ATMP manufacturer) or to the control of the processing facility staff. The collection facility staff and the courier/processing facility staff must sign against their activity in the handover process, and the collection staff member must confirm that the starting material has met pre-determined release criteria. If it has not, the starting material may be released by exception so long as an urgent medical need is justified and documented. The documented handover of the starting material forms part of the permanent record of the collection episode.

Information on the collection bag label, the accompanying documentation and the outside of the distribution box must conform with all relevant data protection regulations; UK data protection regulations apply in the US and in the EU. The collection and processing facilities and ATMP manufacturer must agree in advance the extent of PII that must accompany the collection at distribution.

*A collection episode summary is **communicated** to the referring team, family doctor and ATMP manufacturer*: details relating to the donor whilst undergoing collection, should be forwarded to the referring team, the donor's family doctor and the ATMP manufacturer or local processing facility (as applicable). Information on whether or not long line microbiological culture samples were taken should be included. There must be a process in place to ensure that culture results are communicated to the referring team, ATMP manufacturer and processing facility (as applicable) in a timely manner and consistent with data protection regulations. The collection and processing facilities and ATMP manufacturer must agree in advance which information relating to the collection episode is relevant to the onward manufacture of the cellular therapy product.

Adverse events associated with the collection episode *should be recorded, reviewed and reported.* There should be a defined process detailing the reporting to the HTA of any serious adverse events or reactions occurring during the collection episode, as required by the Human Tissue (Quality and Safety for Human Use) Regulations 2007 (as amended). Details must be shared with the referring clinical team if the donor has undergone collection as part of a clinical trial.

The donor undergoes post-collection ***follow up*****:** the referring clinical or donor team and the collection facility should agree in advance who will carry out post-collection follow-up of the donor to ensure that they have not experienced any untoward side effects attributable to the collection episode, and should also include the opportunity for a donor to report any signs, symptoms, or information not disclosed during the health screening that may render the donation unsuitable. The follow-up also ensures that post-collection blood parameters are within acceptable limits. Patients will be undergoing regular follow-up as part of their standard management plan and so this activity can be incorporated into the clinical team's routine review process.

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Table 1. Regulatory, Accreditation, and Guidelines Frameworks

PROCESS	ORGANISATION	GUIDANCE DOCUMENT	COMPLIANCE (voluntary / mandatory)
Donor Selection	**HTA**	**TSQR 2007**	**Mandatory**
	EUTCD	**EU Directives:** 2004/23/EC; 2006/17/EC; 2006/86/EC	**Mandatory - NI** **Voluntary - GB**
Collection	**HTA** (Human Tissue Authority)	Human Tissue (Quality and Safety for Human Allocation) Regulation 2007 (as amended) HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment[6]	**Mandatory**

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		HTA Codes: A (Consent) E (Research) – not applicable in Scotland G (Allogeneic Bone Marrow and Peripheral Blood Stem Cell Donation) **Montgomery v Lanarkshire Health Board [2015] UKSC 11** **(11 March 2015)** **Mental Capacity Act (2005)** **Adults with Incapacity (Scotland) Act 2000**	**Mandatory in Scotland** **Mandatory in Scotland**
		EU Directives: 2004/23/EC; 2006/17/EC; 2006/86/EC	**Mandatory - NI** **Voluntary - GB**

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	FACT-JACIE (Foundation for the Accreditation of Cellular Therapy-Joint Accreditation Committee of ISCT and EBMT)	**FACT-JACIE International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, an Administration**[7]	**Voluntary**
Labelling and Coding		**ISBT 128 using ICCBBA Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions**[8] **Eurocode-IBLS**[9] **SEC: Commission Directive (EU) 2015/565 amending Directive 2006/86/EC (published 09 April 2015)**	**Mandatory** **Mandatory in NI but not GB** **Mandatory in NI but not GB**
		ISBT 128 STANDARD Labeling of Collection Products for Cellular Therapy Manufacturing Version 1.0.0 November 2020	**Voluntary**
Data Protection	**OIC** (Office of the Information Commissioner)	**Data Protection Act 2018**	**Mandatory**

Recommended documents to consider as part of risk assessment for the product:

- SaBTO Advisory Committee on the Safety of Blood, Tissues and Organs
    - Donation of Starting Material for Cell-Based Advanced Therapies: a SaBTO Review[10]
- SaBTO microbiological safety guidelines[11]
- Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC)[3]
    - Guidelines for the Blood Transfusion Services in the United Kingdom: Bone Marrow and Peripheral Blood Stem Cell Donor Selection Guidelines for Unrelated Donors (Haematopoietic Progenitor Cells)
    - Geographical Disease Risk Index: Guidelines for the Blood Transfusion Services in the United Kingdom (Haematopoietic Progenitor Cells)

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4. Collection of Starting Materials

A survey of JACIE accredited apheresis centres in the UK was undertaken with the aim of identifying current practices and to make recommendations for guidance on mononuclear cell (MNC) collection settings and endpoints.

4.1 Survey methodology

An electronic survey was sent to 36 UK collection facilities to complete online. Follow-up telephone surveys were undertaken with the units that did not respond and some units provided the information in an alternative format. The survey looked at practices around MNC collections including peripheral blood haematopoietic stem and progenitor cells, donor lymphocyte collections, and collections for ATMP manufacture. The survey included questions on the apheresis machine software, and the settings and endpoints used for the different types of procedure.

The survey had a return rate of 80% (29 centres) and included the majority of major collection facilities accounting for approximately 70% of MNC collection procedures in the UK *per annum*. The results included feedback from the initial 9 National Health Service (NHS) sites identified to provide the two currently commissioned Chimeric Antigen Receptor T-Cells (CAR-T) products and all but one of the centres subsequently identified in the second wave who have either applied for or been accredited by JACIE, as well as a number of centres who indicated undertaking starting material collections for CAR-T or other ATMP manufacture for clinical trials. The remaining non-responding facilities are small or very small in terms of numbers of collection procedures performed, and in the main, perform autologous haematopoietic progenitor and stem cell collections only.

The survey results show a general consistency in practice within a relatively narrow range of machine settings and procedure endpoints. Note the recommendations below, or deviations from these, should be fully validated.

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4.2 MNC/CMNC programme

At the time of writing all facilities in the UK use the same apheresis technology for the collection of MNC for ATMP manufacture, the Terumo BCT Spectra Optia® device, although there are two software options available for the device, the MNC collection programme and the Continuous Mononuclear Cell (CMNC) collection programme. Both the MNC and CMNC protocols are valid collection platforms and require staff training and process validation.

Of the 29 collection facilities, 28 (97%) use the MNC programme, 6 (21%) also use the CMNC programme and one facility uses only the CMNC programme for all procedures. Five collection facilities (17%) indicated using CMNC for CAR-T or other ATMPs but these facilities are not all procuring starting material for commissioned products.

Reasons for using the CMNC programme over the MNC programme in these 7 facilities were mainly:

- Collection results for CAR-T and ATMPs
- Reduction in procedure time
- Consistency and control of collection volume
- Selection based on patient blood results
- Numbers of procedures
- Patient size, i.e. paediatric patients.

One facility which uses both programmes indicated there was no determining factor for which one was used.

There is some variance between centres in the starting collect pump flow rate used in CMNC (1.0 mL/min to 1.2 mL/min), some collection facilities using the machine default of 1.0 mL/min. Nevertheless, all facilities using CMNC said they may alter the collect pump flow rate to optimise the collection. In addition, one facility added that they would also make changes to the inlet pump flow rate dependent upon the patient's tolerance of the procedure.

It is recommended that collection facilities procure starting materials for ATMPs using the programme (MNC or CMNC) with which they are most familiar to optimise the collection yield. Where an ATMP manufacturer requires the facility to use a different programme to their standard programme, there should be discussions with the ATMP manufacturer to avoid

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issues of deviation from SOPs and suboptimal collections. Any amendments to the collection programme need to be validated.

Where the CMNC programme is used, the apheresis system manufacturer's default collect pump rates should be adopted unless validation of cell collection has been undertaken at different rates. Guidance from the apheresis system manufacturer is available and should be used to make alterations to the default collect pump flow rate value to meet particular requirements and optimise performance.

4.3 Anticoagulation

All collection facilities use acid citrate dextrose solution A (ACD-A) in compliance with the Spectra Optia® certification.

The survey found that most facilities configure their devices to use an Inlet : Anticoagulant (AC) ratio of 12 : 1 for all procedures (Appendix A, Figure S1). The facilities routinely using a ratio of 13.5 : 1 are multiple facilities in the same organisation which follow a single national SOP. The facility reporting variable ratios for CAR-T collections said they were sometimes 12 : 1, sometimes 10 : 1 and sometimes 8 : 1. For other ATMPS, all facilities used the 12 : 1 ratio.

When asked if the ratio for starting material collections for CAR-T was dependent on the ATMP manufacturer's protocols, six facilities agreed and seven disagreed. Of those facilities that agreed, the range was 12 : 1 for three, 12 : 1 for one which would reduce the ratio if platelet clumping occurred, 12 : 1 to 8 : 1 for two facilities. Similarly for facilities procuring starting material collections for other ATMPs, two facilities stated the ratio was ATMP manufacturer dependent and four stated that it was not, with ranges of 12 : 1 and between 8 : 1 and 13.5 : 1.

Only 7 facilities said they do not adjust the ratio, whereas 22 facilities said that they do. Reasons given were mainly platelet clumping (17 centres). One facility said it would make alterations if the patient was on a treatment dose of anticoagulation and one that uses a ratio of 8 : 1 said it would alter the ratio if the patient had a platelet count of 50–100x10^9/L.

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Although there was some indication by respondents that the initial Inlet : AC ratio used for MNC collections for CAR-T manufacture was protocol dependant, there was a range of ratios used and it was indicated that, in all collections, ratios are changed during procedures to manage issues such as platelet aggregation.

There would appear to be little reason for ATMP manufacturers' protocols to stipulate a ratio as facilities alter the ratio during the collection to manage procedural issues. Responses indicated that the lowest Inlet : AC ratio used to manage platelet aggregation was 8 : 1 which is in line with the apheresis system manufacturer's recommendations.

AC infusion

The AC infusion rate settings ranged between 0.8–1.2 mL per minute per litre of Total Blood Volume (TBV) across all procedures with most facilities running AC at 1.1 mL/min/L of TBV (Appendix A, Figure S2). None of the facilities indicated that this setting was dependent on ATMP manufacturers' protocols for CAR-T or other ATMPs. Most facilities indicated that this setting is not routinely adjusted, but some noted that it varies automatically with reductions of inlet flow. Where centres did indicate adjustments, reasons given were low body weight and citrate toxicity symptoms. One centre indicated it may be adjusted where meeting targets is challenging. Adjustments above 1.2 mL/min/L of TBV were undertaken in small body weight patients where pump speeds of 10 mL/min could not be achieved in the MNC programme, and indicated that prophylactic calcium would be administered. Increasing the rate above the safe limit of 1.2 mL/min/L of TBV reduces procedure time but increases the risk of citrate reaction so requires calcium administration to prevent citrate toxicity.

It is recommended that ACD-A should be used for procedures using the Spectra Optia® as per the apheresis system manufacturer's recommendations and machine certification.

The apheresis system manufacturer's default Inlet : AC ratio of 12 : 1 should be used to commence procedures and Inlet : AC ratio ramping should be switched on in MNC collections. This is the starting point but ratios may be changed during the procedure for optimisation of the collection. The range of Inlet : ACD-A ratios used should be within the apheresis system manufacturer's guidance range of 8 : 1 to 15 : 1. Use of Inlet : AC ratio outside this range is possible in exceptional circumstances but the reasons for doing so must be clearly understood.

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The apheresis system manufacturer's default AC infusion rate should be used and the AC rates should be within the manufacturer's recommended rates of 0.8–1.2 mL/min. Use of rates outside of this range should be validated and rates above 1.2 mL/min must only be used in conjunction with administration of calcium supplement and monitoring of calcium levels.

These anticoagulant recommendations are for standard adult collections. Special considerations will apply to small children with a TBV <1000 mL (see Section 5: Paediatric considerations).

4.4 Total blood volumes processed

The majority of centres use a multiple of TBV as an endpoint for procedures. The vast majority of centres process 2–3 TBV. A small number specified time as an endpoint, often related to specific product pick up times.

The majority of centres did not specify having a minimum or maximum product volume requirement for any product but a few did report minimum and maximum figures for HSPC and donor lymphocyte infusion (DLI) collections because of local laboratory requirements or restrictions. Some CAR-T and other ATMP protocols stipulate a minimum autologous plasma collection volume and a maximum collection volume (Appendix A, Table S1).

The biggest variance was in facilities where a set time endpoint was used rather than a set TBV processed. Collection time ranged from 186 minutes (3.1 hours) to 390 minutes (6.5 hours). Reasons for time endpoints for collections were given as to achieve target cell yields in single collections where products were being transported directly to the ATMP manufacturer; courier pick-up times in these cases were fixed.

For CAR-T collections 8 of 11 centres indicated that endpoints were ATMP manufacturer protocol dependent and 3 stated they were not. For other ATMPs 4 of 7 centres indicated endpoints were protocol dependent and 3 stated they were not.

It is recommended that collection volumes should be calculated by the Optia® based on validated machine settings. Any adjustments to the collected volume through changes made to machine settings must be undertaken in accordance with the apheresis system

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manufacturer's recommendations and validated. Reductions made to either volumes processed or procedure times must not be detrimental to achieving the target cell yield.

In most cases, collections using a target of 2–3 TBV provide adequate cell numbers for ATMP manufacturing (based on preliminary data on non-mobilised collections).[12] However, in some circumstances (e.g. in autologous collections from heavily pre-treated patients, or where higher cell doses are required for manufacturing) it may be necessary to process more than three TBV, where feasible and safe to do so. When performing collections to achieve a specified target cell count, pre-apheresis haematology results and the collection efficiency can be used to inform the number of TBVs to be processed to achieve the required cell number. At all times, attempts should be made to minimise collection times while achieving the required cell dose. TBV and procedure time endpoints should both be recorded to allow for ease of comparison of collections.

4.5 Chamber flush and chase settings

Please refer to Appendix A, Figure S3(a-c). In collection facilities using the MNC programme, flush volumes were consistent across the various procedures with most centres using a flush of 16 mL (27/28 centres, 96%). However, chase volumes varied between 2 mL and 4 mL with, for example, seven centres using 2 mL and 17 centres using 4 mL in PBSC collections. There was greater variation between the centres and in the different procedures in whether the final flush and chase were increased and, if so, by how much. One centre indicated a final flush of 36 mL in low body weight patients to achieve a final volume of 40 mL. This is not consistent with the apheresis system manufacturer's recommendations and will result in a reduced collection efficiency and increased cellular contamination with non-target cells. The chamber flush should be set at 16 mL and the chamber chase at 4 mL.

4.6 Determination of machine settings

Only eight respondents indicated that machine settings were determined as part of a validation despite 24 respondents indicating that they were determined by their organisation's policy. A further eight indicated that settings were determined by the ATMP

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manufacturer's product or trial protocols. It is unclear if protocol settings have been validated where they are different from the validated settings normally used. The HTA and JACIE both require collection processes to be fully validated.

It is recommended that machine settings should be in line with the apheresis system manufacturer's recommendations and must be validated as part of the quality management process. Any changes to validated settings must also be validated.

4.7 Patient, procedure and collection efficiency data

Please refer to Appendix A, Table S2. Cell counts should be available for all collection procedures to allow facilities to meet the requirements of their accreditation and regulatory bodies, and to allow procedures to be optimised in the best interests of patients (and, where applicable, donors). The collection facilities should take samples from the collection bag sample bulbs and obtain counts in-house through their laboratories to verify efficiency of the collection procedure.

All collection facilities should record a minimum set of data:

- diagnosis
- weight and height
- peripheral blood leucocyte count
- peripheral blood target cell count
- haematocrit
- platelet count
- TBV
- volume processed
- procedure time
- collection bag target cell count (yield)

All facilities should receive information on minimum target yield requirements, patient (or donor) pre-collection peripheral blood target cell counts, and collection yields as calculated by the ATMP manufacturer. The collection bag must be sampled through the bulb and the

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yield calculated to serve as a record of the product content before it leaves the control of the collection facility. All collection facilities should calculate machine collection efficiencies.

4.8 Central venous access device

A total of four collection facilities undertaking CAR-T collection and one undertaking other ATMP collections indicated routine use of central venous access devices (CVAD) for procedures. CVAD use in paediatrics was indicated as routine for other collection procedures too. Reasons given for routine use in adults were:

- lack of access to urgent CVAD insertion service
- to maintain stable collection interface
- need to obtain collections on specific dates.

Most facilities indicated that they do have access to urgent CVAD insertion if required, however, three centres undertaking CAR-T and three centres undertaking other ATMP collections indicated no access to urgent CVAD placement.

Peripheral vein assessment should be carried out by experienced apheresis staff prior to collections and if venous access is poor or questionable, arrangements should be made for a CVAD to be placed prior to collection. If time is critical e.g. if the collection must be completed in a single day and go directly to the ATMP manufacturer, or the apheresis centre does not have access to a rapid urgent line placement service, consideration should also be given to an elective line insertion.

4.9 Starting material labelling and documentation

Collection processes for ATMPs were reported as differing from normal practices by six collection facilities. This includes different and additional paperwork and forms, different Identity (ID) checking requirements and different requirements to label product bags before the start of collections. Some facilities reported issues around collection settings, product labelling, documentation, packaging, and staff training. The additional paperwork and time

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required to complete extra documentation for these procedures was felt to be excessive and more likely to lead to transcription errors.

All facilities reported having documentation and ID checking processes which are consistent with accreditation requirements and already capture the information required by the CAR-T and other ATMP manufacturers. Facilities indicated that training by ATMP manufacturers was sometimes delivered by people who were not knowledgeable in apheresis and, as facilities were already trained in apheresis collection, training by ATMP manufacturers took up a lot of time with little or no new knowledge gained.

Facilities undertaking CAR-T and other ATMP collections indicated that labels are sometimes supplied by the ATMP manufacturer for application to the collection pack. Some of the labels supplied by the commissioned and clinical trial ATMP manufacturers are not compliant with the requirements of HTA and JACIE. This results in a requirement for the collection facilities to undertake additional labelling procedures in order to make the collections compliant with regulatory and accreditation requirements.

Recommendations on standardisation of labelling are addressed in Section 7.

4.10 Summary

Overall the results indicate that many facilities use similar settings and are those generally recommended by the apheresis machine manufacturer and/or set as part of a validation process. A small variance exists within the settings for procedure length used for collections for ATMP manufacture, especially those products to be collected in one procedure only and shipped directly to the ATMP manufacturer. The protocols from ATMP manufacturers generally allow collection facilities to follow their own SOPs regarding machine and procedure settings, except in relation to processing blood volume where there are ATMP manufacturer-specific requirements provided in most protocols. Nevertheless, the survey results generally indicate that it is possible to negotiate around TBV to be processed based on the patient's or donor's size and condition, and as such the ATMP manufacturer's desired volume to be processed can be revised. Of note is that generally ATMP manufacturers have not taken paediatric requirements into consideration in their recommendations around blood volumes

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to be processed and it is recommended that ATMP manufacturers must take into account the varying size and weight of all their patients (including children) and provide guidance to account for smaller patients where the collection volume is unfeasible.

5. Specific Considerations for Paediatric Patients

Apheresis procedures for cell collections in paediatric patients are technically similar to those carried out in the adult population. However, there are specific technical challenges when carrying out these procedures in children and young people that are not encountered when carrying out similar procedures in adults. These include securing adequate venous access, maintaining intravascular volume with a small TBV relative to the circuit extracorporeal volume (ECV) , avoidance of fluid overload during the procedure, potential citrate toxicity and the compliance of the child.[12-14] Managing these challenges will facilitate optimisation of the collection procedure and minimise the potential risks to the child when undergoing an MNC collection procedure. For the purposes of this report, a paediatric patient should be considered a child or young person up to the age of 18 years, consistent with the age limit for admission to the United Kingdom's Children and Young People's Services units.

5.1 Patient factors

Similar to adult patients, aspects of the child's disease and past treatment including multiple rounds of chemotherapy, bone marrow and central nervous system disease, prior HSPC transplant or radiotherapy, can be associated with low peripheral blood MNC counts which could then compromise target collection yields. Thus, like adults, optimisation of the child's pre-collection preparation and of the procedure will ensure all steps have been taken to optimise the collection episode and achieve the target yield in patients with low starting cell counts.

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5.2 Psychosocial development

It is important that practitioners are aware of the cognitive and developmental level of the child or young person to ensure their holistic needs are met. Age-appropriate information sharing with children, young people, and their families, will help support the collection procedure.[13-15] MNC collection procedures must be undertaken within an age-appropriate setting which may necessitate the procedure being carried out within the patient's primary treatment centre and not within the adult apheresis unit.

5.3 Citrate-based anticoagulant and flow rate considerations

The citrate-based anticoagulant ACD-A is the anticoagulant of choice for apheresis procedures (Section 4.3). It is metabolised in the liver and excreted by the kidneys. The paediatric group undergoing ATMP MNC collections may have hepatic dysfunction due to previous intensive treatment and this should be considered when setting apheresis collection parameters in individual patients to allow for impaired citrate metabolism. It is important for practitioners to understand the electrolyte and metabolic status of children, particularly in low body weight patients. Appropriate blood chemistry values should be assessed prior to each procedure especially calcium, magnesium, and potassium, as calcium and magnesium are chelated by the citrate anticoagulant during the procedure.[16] Pre-procedure testing will identify those children whose levels are reduced and in whom correction should be undertaken. Young children normally have a diet high in calcium-rich foods so emphasis on foods high in calcium in the days directly prior to and during the procedure can be encouraged.

Few reports or evidence-based guidelines exist on the prophylactic use of calcium infusion in children and careful consideration and education around calcium management is advised.[15] Because of the potential for an increased risk of citrate reactions in children, the use of calcium replacement as required is commonplace.[13,17,18] However, calcium replacement is not necessarily required intravenously, and oral supplementation[19] is supported within the literature as there is no consensus on the route of calcium administration within the paediatric population.[15,20]

Monitoring of pulse rate, oxygen saturation, blood pressure, temperature and respiratory rate should be undertaken throughout the procedure as a general patient safety measure and

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also to allow early detection of possible citrate toxicity, particularly in young children who are not able to verbalise. Common signs and symptoms of chills, abdominal pain, emesis, pallor, bradycardia and hypotension may also indicate citrate toxicity,[14,16] and local management policies should be followed if citrate reactions do occur.

5.4 Total Blood Volume, Extracorporeal Volume and Blood Prime

Practitioners must consider the ECV and how this relates to the child's TBV. The MNC and CMNC collection programmes have different ECVs and reference to the apheresis system manufacturer's guidelines for blood priming is advised when ECV is greater than 10–15% of the child's TBV.[17]

Local guidelines should be established in relation to patient weight ranges for blood prime when the ECV is greater than 10–15% of the patient's TBV.

Pre-collection haemoglobin optimisation is one factor that contributes to steady flow rates and so establishment of a stable interface and yield optimisation. A blood prime in a small low weight patient will promote haemodynamic stability.

For example, some centres may wish to consider ensuring that on the day before the planned procedure, the child's haemoglobin is maintained above 100 g/dL[20,21] using red cell transfusion as required to achieve a pre-collection haemoglobin of 100–120 g/L. However, lower pre-collection haemoglobin levels may be preferred and pre-collection haemoglobin optimisation can be consistently achieved by developing age-specific protocols for transfusion thresholds based on local experience. Such protocols will result in optimisation of yields while not compromising patient safety.

5.5. Impact on Inlet Flow Rate - Venous Access

Another important factor in optimising collection efficiency is the appropriate selection and insertion of venous access devices. Where possible, peripheral access should be utilised, but in children, insertion of a temporary CVAD may be required. The priority should be to establish a steady flow rate that allows the collection to proceed without interruption.

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Practitioners may have to accept a constant, although potentially slower, flow rate over a faster flow rate with interruptions secondary to vasospasm and associated pressure alarms. This will extend the procedure time but will optimise the collection efficiency and may enable the cell dose to be collected in one procedure.

Optimisation of venous access must also be prioritised as there may only be a small collection window.

Venous Access Options

- Large bore peripheral cannula for draw line with a single lumen of a Hickman line for return
- Apheresis system manufacturer's access needle from disposable set (draw line) and large bore cannula for return
- Temporary central venous catheter suitable for apheresis – femoral insertion and not subclavian or jugular should be considered
- Ultrasound-guided deep vein cannulation in age-appropriate patients.

The potential risks to the patient of having a temporary wide-bore double lumen central venous catheter suitable for apheresis should be considered. The risks can be mitigated by femoral line placement under expert interventional radiology control,[14,22] and the requirement for cell collection in this patient group to enable further treatment should be balanced against line insertion risk.[15,19]

Optimisation of inlet flow rates in part through adequate venous access will result in:

- improved collection efficiencies
- optimisation of the procedural run time and associated reduction in exposure of the child to the procedure, and
- exposure of the child to less citrate and so less likelihood of hypocalcaemia.

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6. Processing and Storage

6.1 Processing

The starting material may require processing and/or storage at the local processing facility prior to onward distribution to the ATMP manufacturer. Documentation containing Chain of Custody (COC) and Chain of Identity (COI) information and validated processes must be in place for either process (see Section 7).

The following steps must be considered to allow optimum processing and storage of starting materials for further manufacturing and may require additional internal qualification and approval from licensing authorities if an adjustment from established practice is required. Note the HTA require all processes to be covered by an approved Preparation Process Dossier.

Validated conditions must be in place for the storage of fresh starting materials. Storage is primarily at 4±2 ^{0}C in a monitored/alarmed blood fridge, but some ATMP manufacturers may specify other conditions where local validation would be required. To reduce cellular stress the total leucocyte concentration of the starting material should be below 200 x 10^{9}/L and onward distribution or cryopreservation should take place within 48 hours of collection.

Some ATMP manufacturers may not permit sampling of the product to assess the cellular content. However, collection efficiencies must be audited to ensure that the collection facility complies with JACIE requirements; sampling should be carried out using predetermined procedures, agreed in advance with the ATMP manufacturer, and specified in the Quality Technical Agreement (QTA) (see Section 9).

6.2 Cryopreservation

Where cryopreservation is required prior to onward distribution to the ATMP manufacturer, several steps need to be considered:

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- Any additional processing steps required prior to cryoprotectant addition, e.g. a wash, volume reduction or concentration step
- Cryoprotectant concentration
- Protein source e.g. autologous plasma, Human Albumin Solution (HAS) etc.
- Passive freeze or Controlled Rate Freeze
- Verification of an adjusted freeze rate programme (with or without compensation for the eutectic point)
- Validation if the sample volume/container/cryobag size is varied
- Cryostorage temperature limits and high alarm triggers.

Post-thaw viability assays should form part of the validation of the cryopreserved starting materials but this assay alone does not guarantee functional activity, which may be considered as a complementary test.

Cryopreservation of the starting material introduces greater security and flexibility to the logistics step. Cryopreservation is the process of cooling material from ambient to below manufacturer's specification. This process must be conducted in a controlled manner to ensure the best recovery of cell number and phenotype when thawed at the manufacturing site. There are established methods for cryopreservation; these methods and the science behind them are reviewed here.[23-26] Until recently the equipment required for obtaining and maintaining cryogenic temperatures was dependent on liquid nitrogen (LN_2). However, technology is now available that enables cryopreservation and storage below -120 °C without the need for LN_2, opening the possibility for clinics not LN_2-enabled to be considered for the treatment of patients with an ATMP product where cryopreservation is required.

If cell cryopreservation is required at a processing facility prior to shipping to the manufacturing site, a competency assessment should be conducted and approved. The approved processing facility procedures will usually be followed although sometimes ATMP manufacturers may request amendments to these. An amended protocol would need to be fully validated prior to use. Cells will subsequently be packed into a cryogenic shipping container for immediate shipment or in a cryogenic storage unit for later shipment. The

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cryogenic shipper and cryogenic storage unit should be qualified and validated respectively prior to use.

A cryopreserved starting material will need to be thawed before the manufacturing process can begin. Thawing is as critical to cellular integrity as cryopreservation.[26]

When the starting material, fresh or cryopreserved, leaves the control of the collection facility, validated distribution methods must be used, with roles and responsibilities agreed in advance between the processing laboratory and the manufacturer (Section 8). Storage conditions must be defined and actions agreed if storage conditions fall outside of predetermined specifications (Section 6). The processing laboratory quality assurance QA must confirm that the starting material has met pre-determined release criteria and export licensing if applicable. COC must be maintained following handover to the courier.

7. Labelling and Traceability

7.1 Initial labelling of starting material

7.1.1 Standardisation

The labelling of starting material must be optimised to provide a robust procedure for traceability. Most UK and EU apheresis centres involved in the collection of cells as starting material for ATMP manufacture must be using labels which meet the EU and FACT-JACIE requirements and this entails the use of the ISBT 128 standards and/or the SEC code. These have already been accepted as the international standards for the standardisation of labels. The donation identification number (DIN) and Single European Code (SEC) ensure the donation is unique and provides a basis for traceability. The use of the SEC is a requirement in NI and the EU, but no longer in GB.

7.1.2 ISBT 128

ISBT 128 is the international information standard for the terminology, coding and labelling of medical products of human origin. It was developed by the International Society of Blood

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Transfusion to provide an international standard for the terminology, identification and labelling of donated blood for transfusion and has been expanded to cover all medical products of human origin, and is now used in over 87 countries worldwide. Having a standard labelling system enables identification and information about biological products using standard terminology which can be exchanged between different computer systems. This needs to be the aim for the labelling of ATMPs if we are to ensure traceability throughout the collection, processing, transport, manufacture, and final product.

ISBT 128 specifies:

- A donation numbering system that ensures globally unique identification
- The information to be transferred, using internationally agreed reference tables
- An international product reference database
- The data structures in which this information is placed
- A barcoding system for transfer of the information on the product label
- A standard layout for the product label
- A standard reference for use in electronic messaging.

The standard has gained international acceptance and is now in widespread use. Following meetings between FACT, JACIE, and the International Council for Commonality in Blood Banking Automation (ICCBBA), an agreement was reached to support the use of ISBT 128 for coding and labelling products of human origin. This decision has been endorsed by the Boards of relevant major professional organisations.

7.1.3 The ISBT 128 cell therapy products label

The use of an ISBT 128 cell therapy product label standard ST018, ISBT 128 Standard Labeling of Collection Products for Cellular Therapy Manufacturing v1.0.0,[5] provides international consistency to support the transfer, traceability and transfusion/transplantation of blood, cells, tissues and organs.

The product label contains:

A unique Donation Identification Number (DIN)

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The use of an ISBT 128 provides a method for unique identification of any donation worldwide by using a 13-character DIN built up from three elements: the first element identifies the country and the facility that assigned the DIN (e.g. the collection facility, registry, etc.), the second element defines the donation year +/- one month, and the third element defines a unique sequence number controlled and maintained by the facility that assigned the DIN. The combination of the alphanumeric DIN elements ensures that the donation number is truly unique.

Facility codes are assigned by the International Council for Commonality in Blood Banking Automation (ICCBBA), who maintain a database of all registered facilities.[8] A lookup programme allows the identification of individual facility codes. ICCBBA licensed facilities and vendors are able to access these via the ICCBBA web site.[8]

The label has been developed to conform to ISBT 128 and also to include a standard coding system for the manufactured product, by using COI designation to be included as a COC identifier.

Product codes

The standard system for ISBT 128 product codes is constructed by international consensus to ensure global consistency in use and understanding. The standard terminology is maintained on the ICCBBA website and is publicly available. Cellular product terminology and coding is managed by ICCBBA and the International Cellular Therapy Coding and Labelling Advisory Group (CTCLAG). New products are defined by combining pieces of information from the standardised terminology in a way that unambiguously describes the product. This process is made easier by the use of the concepts of a component class, core conditions, and attributes. The combination of the DIN and Product Code will identify a specific bag of product, including cell starting material and intermediates.

7.1.4 The SEC code

All procurement of tissues and cells for human use in the UK must take place under the appropriate licensure (usually an HTA licence) and there is a legal requirement for an identifier for all tissues and cells which is unique to each procurement and must be on the label if there

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is sufficient space (it must accompany the product if not). The SEC includes the country of origin, Tissue Establishment number, the unique donation number (this is the same as the ISBT 128 DIN), the product code and its division number, and the expiry date. This may no longer be required in GB but is necessary for materials collected in NI and the EU.

Structure of the Single European Code

Donation Identification sequence **Product Identification sequence**

EU TISSUE ESTABLISHMENT CODE		UNIQUE DONATION NUMBER	PRODUCT CODE		SPLIT NUMBER	EXPIRY DATE (YYYYMMDD)
ISO Country Code	Tissue Establishment Number		Product Coding System Identifier	Product Number		
2 alphabetic characters	6 alpha-numeric characters	13 alpha-numeric characters	1 alphabetic character	7 alpha-numeric characters	3 alpha-numeric characters	8 numeric characters

The SEC can be derived from the ISBT 128 product terminology or from the Eurocode product codes and the preceding letter signifies which system has been used.

When the product code and/or the expiry date changes, or a product is split into different divisions a new SEC will need to be generated and applied, but the Centre details and the unique donation number will remain constant, ensuring the harvest can always be traced to its origin.

7.1.5 FACT-JACIE International Standards for Haematopoietic Cellular Therapy Product Collection, Processing and Administration

These standards apply to all phases of collection, processing, storage, and administration of haematopoietic cellular therapy products. This includes HSPCs, MNCs and IECs derived from the bone marrow, apheresis or cord blood. Most collection and processing facilities involved in procuring starting materials for ATMP manufacture will need to be accredited by FACT-

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JACIE. The FACT-JACIE standards stipulate that the ISBT 128 labelling system must be used for the labelling of apheresis products.

In the current FACT-JACIE Standards (seventh edition) a significant change was made to include the statement: '*Labelling elements required by applicable laws and regulations shall be present. Implementation of ISBT 128 terminology, identification, coding, and labelling is required unless Eurocode has been previously established and maintained. FACT and JACIE recognize the significant benefits of international standardisation of coding and labelling in cellular therapy, and support the international efforts to implement ISBT 128 and Eurocode. ISBT 128 is the global standard for terminology, identification, coding, and labelling of medical products of human origin, and has been designed to ensure accuracy and safety for the benefit of patients and donors worldwide.'*

The draft eighth edition of the standards has changed the definition of cellular products to:

'Somatic cell-based product (e.g. mobilized HPC, mononuclear cells, cord blood cells, mesenchymal stromal cells, T cells, natural killer cells) that is procured from a donor and intended for processing and administration, to include IECs, gene-modified cells, and other cellular therapies.'

It specifies that starting materials for ATMP manufacturers shall be labelled with product labels that conform to FACT and JACIE requirements and applicable law. This will in effect mean that the labels that collection centres currently use (i.e. ISBT 128 compliant labels) must also be used for all cells procured as starting materials for ATMP manufacture.

7.2 Labelling Collections to Meet ATMP Manufacturer Requirements

7.2.1 The current position

The current situation with regards to the labelling required by clinical trial sponsors and ATMP manufacturers is very different in that there are no set standards and no fixed set of information required. Some ATMP manufacturers are happy for the collection facility's existing procurement labels to be used, others have begun to ask for the DIN and SEC to be included, and some request extra data, whilst some insist on collection facilities applying the pre-printed labels they provide. However, a pre-printed label cannot contain SEC as it is

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generated by the facility executing the collection at the time of the apheresis. Moreover, adding a pre-printed label does not preclude adding regulatory compliant labelling. Pre-printed labels thus do not meet any of the regulatory requirements. The application of a SEC code to a product for import to the EU or NI should, if possible, be applied at the point of procurement or, if this is not possible, by the importing organisation.

Some of the details requested for adding to labels (e.g. The Principle Investigator, centre number, trial number etc.) could be provided in accompanying documentation, on a separate hangtag, or a small label rather than part of the existing collection label. This method is compatible with the ISBT 128 standard ST-018.

The additional information required varies between ATMP manufacturers and given that some collection facilities will be dealing with large numbers of products involving different ATMP manufacturers, each having their own labelling requirements, this is not sustainable as the number of ATMPs in clinical trials or adoption increases.

At the moment many ATMP manufacturers insist on the avoidance of any patient information on the labels for products collected for use in clinical trials. The collection facilities would typically have this information on the label and most ATMP manufacturers request that this is redacted. The FACT-JACIE standards allow for the donor and recipients name and/or identifier to be used so a donor or trial-specific patient number could be used with the redaction of the other details if required, but not all collection centres would be able to do this easily. Most would prefer to follow their standard practice and to have the patient or donor details on the label for checking when identifying the individual.

Given the confidentiality clauses built into the agreements with the ATMP manufacturer already, it should not prove impossible to allow the use of donor details and to obtain the donor's consent to their details being shared with the ATMP manufacturer if this is necessary.

Labelling presents a substantial challenge. The simplification of label processes and the content will reduce the occurrence of errors and deviations. Standardisation is vital to providing a safe and robust method of ensuring traceability and manufacturers are required to accept that collection facilities must comply with regulatory standards.

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If the codes needed by manufacturers are incorporated within the ISBT 128 standard terminology, this will facilitate the use of one labelling system throughout the process.

However, it is hoped that adoption of the standard ISBT 128 Labeling of Collection Products for Cellular Therapy Manufacturing, approved November 2020, will drive standardisation of information requirements.

7.2.3 Information technology

It is important for label details to be completed electronically wherever possible in order to reduce the chance of transcription errors which could lead to products not being accepted for manufacture. This may be a challenge for some centres, particularly those relying on preprinted labels, but most should already have electronic databases which could be used. There will always be some fields on collection labels which need to be completed manually as the data are not available at the time of labelling e.g. the volumes of product and anticoagulant, and the end time.

The introduction of a new label template is likely to involve input from information technology (IT) companies involved at a local level and will carry a financial cost.

The production of the label template by the ATMP manufacturer is another possibility but would mean having access to donor details and having the corresponding confidentiality clauses in the Quality Technical Agreement (QTA). Some ATMP manufacturers have tried to arrange to print labels remotely at collection sites, but this causes security issues with some IT departments and is not always permitted. It may be possible to print from emailed labels but controls would need to be put in place to ensure the correct labels are sent and printed.

7.2.4 Date format

Currently collection facilities and ATMP manufacturers have different formats and this can cause confusion, especially between days and months - DD/MM/YYYY and MM/DD/YYYY, etc.

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The new ISBT 128 standards ST-018 require dates to be printed in compliance with ISO 8601-2004 numeric extended format [YYYY]-[MM]-[DD]. For example, September 27, 2020 is represented as 2020-09-27.

Times need to be printed based on a 24-hour clock with a colon placed between the hours and minutes. The time zone also needs to be identified.

7.2.5 Label printing

As with IT, individual collection facilitates may be able to use existing printers to produce the standard labels and others may need to invest in new equipment.

7.3 Labels in Manufacturing

As well as being able to trace products back to the collection facility, there is a need to standardise labels at various stages of the manufacturing and to maintain traceability throughout the product's journey. The DIN provides a standardised unique number and enables the identification of a product and traceability to its source. A standardised unique identification number could also be used to identify the manufacturer and this has been covered by the Standards Coordinating Body proposal who have begun to develop a set of standardised COI and COC identifiers. Draft examples of possible hybrid labels have been put forward for consultation. These labels aim to meet the regulatory requirements of the collection facilities as well as the needs of the ATMP manufacturers. The labels bear the patient's details and have a specific area for ATMP manufacturer details.

The addition of the Manufacturer Information area could allow for any specific information required for a clinical trial to be added to the label. This addition would need to be standardised across the sector for it to be worthwhile for collection facilities to incur the additional costs associated with changes to the label set-up.

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Full Label – Cryopreserved Product with No Expiration

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Post Clinical Trial Approval

A9996 20 123458 00 Z

Collection Center
City, State, Country, Postal Code

Collection Date and Time 2020-01-14 13:40

Do Not Irradiate

S1303100

MNC, APHERESIS
For Further Processing

Total Volume ___ mL containing approx ___ mL Citrate

Store at 1 to 10 C

FOR AUTOLOGOUS USE ONLY

Intended Recipient:

Recipient ID: XXN127654
DOE, Charlie Alex
Patient DOB: 1999-06-01

Expiration Date/Time:
2020-01-17 13:40 EST
(2020-01-17 18:40 UTC)

COI: 123ABC456DEF789GHI

Protocol: NCT99999999

Collection Center Site No: 47
Autologous Apheresis for Further Use in Manufacturing of XXXXXX Drug Product

Sponsor Info/Logo Area

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Full Label – Related Donor

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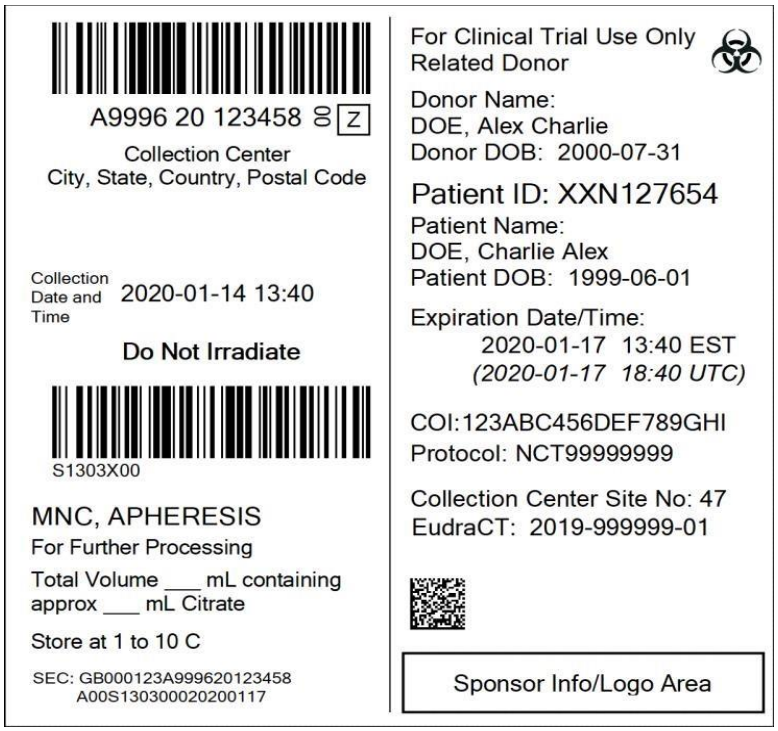

(from: *Labelling of Collection Products for Cellular Therapy Manufacturing V1.0.0, November 2020*).[8]

7.4 Conclusion

The use of the ISBT 128 labelling structure for cellular products is already a requirement for collection facilities and this includes cells collected as starting materials for manufacturing into medicinal products. Collection facilities should therefore use their already standardised labels for the collection bags.

ISBT 128 databases are to be expanded to include specific products from individual ATMP manufacturers and a hybrid label template has been developed to cover both the collection and manufacturing labelling needs and is now detailed in the ISBT 128 standards.

By agreeing a consistent approach to the standardisation of labelling to all cellular products collected as the starting material for further manufacturing, the risk of labelling errors and the misinterpretation of patient data once it leaves the collection facility can be reduced. A standard hybrid ISBT label should be used. Using existing ISBT 128 databases will make it easier for the collection facilities to change their labels and the same label stock, printers and

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product databases can be used. Some facilities have pre-printed label stock and this will prove more of a challenge to them.

Eventually the move to the ISBT standardised label format will enable the use of one standard system for identification of a product and traceability from collection to its final fate, and unique identification numbers used throughout with information pertaining to the current state, while changing the product code depending upon the stage of manufacture.

There will be hurdles to overcome with different technology being used to produce labels by the collection facilities, and moving away from the systems already set up could be costly and difficult to achieve.

8. Transport and Logistics

For the purpose of this section, logistics means the processes by which the ATMP starting material (e.g. a patient's apheresis collection) moves from the bedside to the manufacturing facility where it will be used to start the production of the therapeutic medicine. While the focus here is on the starting material, similar considerations are required for the final product's journey back to the clinical setting.

For autologous therapies in particular, the distributed nature of ATMP supply chains across numerous partners and locations (from the collection facility, through the processing facility, to ATMP manufacturer, and back to treatment centre via a storage facility) makes the coordination of timings and transfer of materials across the partners critical to successful patient treatment.

Because of this intricate complexity, it is necessary for ATMP manufacturers to work essentially as part of an extended matrixed treatment team, aligning with activities both within and beyond the clinical facilities. To this end, manufacturers will often employ dedicated teams of apheresis operations, clinical site interfacing logistics experts and patient schedulers who align clinical apheresis activities with ATMP manufacturing slots. They often coordinate the intervening transportation to maintain CoC, minimise the burden on clinical sites, reduce the chance of deviations, and improve manufacturing turnaround times.

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The act of transferring collected MNC from the collection facility to the manufacturing facility requires coordination of complex supply chain logistics processes. These processes involve sites, equipment, systems, personnel, and third-party couriers. In addition, logistics processes must manage an array of unpredictable and uncontrollable external events such as traffic delay, delayed flights, customs delays, inclement weather, natural disasters, civil unrest, pandemics, etc.

The aim of logistics is to ensure delivery of the critical starting material in a time frame that complies with the validated tolerances of expiry time of the critical starting material. Accountability for compliant logistics is with the manufacturer. The provision of logistics for an ATMP is a critical part of the supply chain and must be performed by qualified subject matter experts.

8.1 Collection facility: pickup and delivery

Manufacture of an autologous ATMP product requires MNC as starting material. Procured cells may be released directly from the collection facility or may be transferred to a processing facility to either cryopreserve or package fresh material. Cells are often transferred using ambient validated temperature transport boxes or shippers, or may be cooled at 2–10 °C.

As soon as cells arrive in the processing facility, the labelling, contents, and condition of the cell bag are inspected. In some cases, a cell sample may be taken as a basic quality check. Cell temperature and expiry (vital to unfrozen material) must be specified and monitored as these are critical parameters for cell viability and manufacturing.

8.2 Transportation couriers

In addition to a courier shipping cells, the courier may provide other equipment, systems and services such as validated shippers, storage, tracking, temperature monitoring, a customs broker, etc. As both the starting material and final drug product are unique and potentially irreplaceable, high-touch and high-supervision systems are typically required. CoC and material integrity need to be demonstrated throughout the vein-to-vein journey for GMP quality systems to deem the final product fit for use. Prior to engagement, the courier must

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be evaluated for capability and approved. Specific handling instructions to maintain cell viability and minimise transportation time must be communicated as a work instruction to the courier. This instruction may indicate priority first flight shipment, hand carry, do not X-ray, etc.

During cell collection scheduling, a courier booking will be made. Typically, submitted information and documentation such as permits, customs invoices, declarations etc., will be reviewed by the courier. The cells may be packed into the validated shipper earlier if a validated shipper is provided in advance by the manufacturer or courier. Otherwise, the cells will be stored under controlled access at an appropriate temperature before being packed, when the courier provides the shipper for pickup. The shipper and documentation are tendered to the courier. The courier ensures that the shipper and courier documentation is in order and will transport the cells to the manufacturing facility. In the event of any delay in the courier service, a contingency plan should be in place in the absence of processing facilities on site.

8.3 Shippers

The protocol should specify a temperature range to maintain while cells are shipped. The validated shipper must be validated for the likely environments it will encounter, particularly if transport will occur in extremes of heat and cold.

Cryogenic shippers require similar care and scrutiny when being selected. Cryopreservation extends the validates expiry time while maintaining the materials integrity. The chosen shipper must be validated to ensure it can reach its destination while maintaining a temperature specified by the manufacturer, typically below -120 °C. The choice of cryogenic shippers span from a ‘standard’ LN_2 dry shipper, to smart LN_2 dry shippers and LN_2-free cryogenic shippers.

The software, tracking, monitoring and services associated with shippers of all temperatures, now allows the ATMP manufacturer to closely oversee the logistics steps. Interconnectivity between the different service providers that come in contact with the logistics process is increasing. For example, ATMP orchestration software can be used to directly book the

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courier. These advances in technology are essential to support the complexity and rapid growth of the industry while maintaining the critical elements of CoI and CoC.

The shipper, any supporting technology, and/or service must be validated fit for purpose. Validation does not guarantee that the specifications will always be maintained. However, it does provide a high level of assurance.

8.4 Routes

A shipping route is the path via which starting materials must be shipped from origin to destination. Routes must be assessed in advance to determine whether risk mitigation actions are needed for reliable and sustainable delivery. This may cover the method of pickup and delivery, shipping by ground or air, permits and clearance documents, route duration, etc. The route used is critical, especially in serving remote and/or international collection sites. These may involve complex logistics and lead-times that could impact cell viability. Actions to assess shipping routes could range from logistics table-top exercises, test shipments and lane qualifications, etc. Many companies mandate a mock shipment to ensure the shipping lanes and a supply chain are feasible.

8.5 Licenses, Permits and Customs Clearances

8.5.1 Import and export licences and approvals

Regulatory and other government agency requirements are dynamic and will evolve as the UK EU Exit policy becomes more mature. The following should be used as a guide where details of the latest requirements are sought from customs experts.

Now that the UK have exited the EU an HTA import licence is needed to import starting material into GB from the EU, or to export starting material from GB to the EU. An HTA import licence would also be needed to import starting material into NI from GB.

Import and export customs requirements again may vary between member states, however all 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 converse

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will require a GB EORI. The UK government customs declaration requirements for substances of human origin used in grafting, implanting or transfusion for imports (page 105) and exports (page 238) of the Border Operating Model is a useful reference point.[27]

Government agencies and or countries may have requirements and/or restrictions for shipping cell material. These may cover Genetically Modified Organisms (GMO), animal-derived, in vivo usage, etc. For cell material to ship without incident, such requirements must be clearly understood prior to shipment as permits may take days to months to obtain.

9. Quality Management, Audit, and Regulatory Compliance

9.1 Regulatory compliance

9.1.1 Starting materials

The starting material for many ATMPs are MNCs procured via apheresis from pre-selected patients that have been tested for mandatory serological and nucleic acid markers for infectious diseases. UK regulation allows for these cells to be procured and the patients to be tested by Tissue Establishments licensed by the HTA under the Human Tissue (Quality and Safety for Human Application) Regulations, (SI 1523/2007) in GB, or under the EU Tissues and Cells Directive (EUTCD; 2004/23/EC) in the EU/NI, or by Blood Establishments licensed by the MHRA under Blood Safety and Quality Regulations 2005 in GB, or the EU Blood Directive (2002/98/EC) in the EEU and NI.

In practice, all apheresis collection sites in the UK procure MNC under their HTA licence and the majority are also accredited to FACT JACIE standards for Hematopoietic Cellular Therapy, administration of IECs, prevailing edition.

Importing and exporting tissues and cells for human application

An establishment in GB that sends (exports) or receives (imports) tissues or cells to or from a country in the European Economic Area (EEA), needs an HTA licence that covers these activities from 1 July 2021.

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The HTA will continue to be the Competent Authority in Northern Ireland for the regulation of tissues and cells for human application. Since 1 January 2021, establishments in NI have been required to treat suppliers in GB in accordance with the relevant EU regulations on non-EU suppliers. This means if you receive human tissues or cells from GB for human use, you will need an import licence and an agreement with the supplier in GB.

An export certificate is required if starting material is to be sent (exported) from GB to NI and the receiving body in NI will need an import licence. Neither body require additional licences to import material from NI into GB.

9.1.2 Scope of the regulations, accreditation and guidance as applied to the collection of starting materials for manufacture of an ATMP

- HTA Guide to Quality and Safety for Human Tissues and Cells for patient treatment 2021[6]
    - Procurement, Donation and Testing
    - Processing and Storage if carried out before shipment to manufacturer
- The UK Orange (GMP) guide or, in the EU, EudraLex Volume IV – Guidelines on GMP specific to ATMPs[28]
- The Pharmaceutical Inspection Co-operation Scheme (PIC/S): GMP Guide Annex 2A[29]
- Accreditation by FACT – JACIE, 7th edition[30]
    - Applicable standards are: C1 to C12
        - Part B sub-section C6 for Donor Selection
        - Part D when processing cells prior to shipment (cryopreservation)
        - Parts D7, 10 and 11 for distribution
        - Appendix II – labelling

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9.1.3 Obligations of the collection facility (both as an HTA licence holder and to the ATMP manufacturer)

Donor Screening and Testing

Mandatory infectious disease marker tests must be validated and conducted for all donors at the time of procurement). It is advised that these tests also form part of the initial screening of the patient/donor so that the downstream ATMP manufacturer can manage risks with respect to cross-contamination and mix up because manufacturing activities often commence before the test results are confirmed. The following tests must be performed: Anti-HIV-1,2; HBsAg; Anti-HBc (when HBc is positive and HBsAg is negative a risk assessment should be used to determine eligibility); Anti-HCV-Ab and *Treponema pallidum* (syphilis) serology. HTLV-1 antibody testing must be performed for high risk patients, and the advice of the UK Government Advisory Committee on Safety of Blood Transplant and Organs (SaBTO)[10,11] recommends that all new allogeneic donors are tested for hepatitis E, toxoplasma, EBV and CMV.

SaBTO also recommends HIV, HBV, HCV and HEV nucleic acid testing and consideration of Parvovirus B19. Additional microbiology requirements may be required where there is a high risk (e.g. due to travel), or where there is a requirement in that regulatory territory (e.g. malaria and WNV).

The Tissue Establishment (TE) should confirm in a QTA with the ATMP manufacturer that these testing requirements are its responsibility, and it will inform the ATMP manufacturer of any information that effects the microbiological status of the patient/donor. Any infectious disease testing of marketing approved ATMPs will be as agreed with the approving regulator.

Collection procedures

Collection by apheresis is a well-established procedure. All procurement procedures must be conducted to minimise risk to the patient/donor and the starting material, and should take place in areas that have been assessed to minimise the risk of microbial contamination of procured cells to acceptable levels. Materials used in testing and procurement should be stored suitably, and where temperature controls are required they should be monitored sufficiently to identify excursions from defined limits.

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For some ATMPs a standard whole blood draw is suitable to obtain the starting materials for the product to be manufactured, and no more than one blood unit (e.g. ~500 mL) should be the maximum procured by the phlebotomist. This procedure would have to be undertaken under the aegis of a Blood Establishment Authorisation.

9.1.4 Obligations of the ATMP manufacturer

Logistics

In agreement with the MHRA, regulatory requirements around the responsibility of transfer of cells to the ATMP manufacturer state that provided the responsibilities of each party are clearly detailed in agreements, this procedure could be covered by either the TE or the ATMP manufacturer. This can be challenging as it is generally the ATMP manufacturer who commissions the specialist courier. Under these circumstances, the TE needs to satisfy itself of the quality and technical elements of the transfer. Such arrangements must form part of a contract, with responsibilities carefully set out in a QTA.

9.2 Quality Management

9.2.1 Quality management system

Implementation of a Quality Management System (QMS) allows collection and processing facilities are required to satisfy multiple regulatory and accreditation requirements. Variation is dependent upon whether the facility is within a hospital or Blood Service and the particular regulatory arrangements that apply.

As a minimum, the TE should operate within a QMS that meets the HTA standards for Governance and Quality, with the following elements:

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- written procedures for all activities in a document-control system
- regular minuted governance meetings covering risk management, quality, and clinical standards
- control and recording of materials used in procurement and testing
- a system for dealing with complaints
- documented agreements with third parties
- audits (both internal and independent)
- personnel induction and training against written job descriptions
- personnel appraisals
- procedures for the management of records
- record review procedures
- the maintenance of a 'tissue register' to facilitate annual activity reporting
- procedures in place for identification and investigation of serious adverse events, reactions, or incidents (SAR/E) and their notification to the HTA
- procedures for recall of cells affected by adverse events
- documented risks assessments for all activities

9.2.2 Quality Technical Agreement

An ATMP manufacturer should establish systems to assess a TE for suitability as a supplier based on the needs relating to the procured starting materials and the ability of the site to provide them. Eligibility is based on the scope of the TE's licence and the activities it will undertake regarding procurement and testing.

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The Manufacturers' QMS requires qualification of the supplier to determine that they are suitable and eligible to procure the apheresis starting material on their behalf. This may include the conduct of a site assessment to satisfy and develop the following:

- Determine that the collection site has a current TE licence where scope includes the collection of MNCs.
- Agree and define technical aspects around the collection including:
  - specification for collection
  - processing steps e.g. cryopreservation
  - labelling and packaging
  - storage awaiting uplift
  - CoC and licensing arrangements.

Once the assessment process has been satisfactorily completed, written agreements defining the relationships and responsibilities of parties can be progressed. The TE has a regulatory responsibility to execute an agreement with any organisation to which it distributes cells for direct human use or transfers cells to another organisation e.g. for ATMP manufacturer (a QTA). The required specification of the apheresis collection should be set out in a mutually agreed Quality Technical Specification (QTS).

The content of these documents (QTA & QTS) should be in accordance with that defined in the HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment 2021, and that of the UK Orange (GMP) guide or in the EU EudraLex Volume IV GMP Guidelines (Part IV GMP, Section 13: Outsourced activities).[28]

The intent of the QTA is to set out the respective responsibilities of the TE and that of the ATMP Manufacturer to ensure that continuing licensing and accreditation obligations are met, and that the activities are clearly delineated ensuring there is no confusion with responsibilities.

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9.2.3 Serious adverse events and reactions (SAE/R)

Respective responsibilities should be set out in the QTA for the reporting of any donation-associated SAE or SARs that may have occurred during the procurement process including notification to HTA. The ATMP manufacturer should accept responsibility of reporting to the TE of incidents during transportation that may impact the quality and safety of the cells, and any defect with the cells that may indicate that an error occurred during procurement, storage, transfer, or processing if performed at the TE (i.e. cryopreservation). The TE remains responsible for SAE/R notification to the HTA.

Feedback on the quality of cells is a JACIE requirement, standard C4.7.1, and a collection facility may ask the ATMP manufacturer to provide information on the outcome of tests undertaken, for example, the phenotypic profile of the MNC population, or viability upon use.

9.2.4 QMS of the manufacturer and audit

It is essential that the manufacturer can assure the quality and safety of the starting material for the purposes of manufacturing an ATMP. The ATMP Regulations require that the manufacturer must evaluate and select third parties procuring tissue or cells (starting material) on their behalf, to satisfy the requirements of the manufacturer's licence.

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Regulatory Framework: where to find relevant standards

Aspect		HTA – TQSR	FACT JACIE 7th edition	GMP Part IV sections
Donor consenting		✓	✓	
Donor screening		✓	✓	
Procurement		✓	✓	
Label content and chain of identity		✓	✓	
Storage conditions		✓	✓	✓
Distribution and chain of custody		✓	✓	✓
Quality Management (selection only or all)?	Audit	✓	✓	✓
	QTAs and content	✓	✓	✓
	SAE/R reporting (including transport-related incidents)	✓	✓	
	Recall and Traceability	✓	✓	✓

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11. Appendix A

Organisation List and Survey Data

1. Organisation List

2. Collection of Starting Materials

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1. Organisation List

Manufacturers	Regulatory Organisations	Clinical Processing Units	Clinical Apheresis Units	
Cardiff UH	Human Tissue Authority (HTA)	Manchester	**Birmingham**	**London**
Achilles Therapeutics	Medicines and Healthcare products Regulatory Agency	NHSBT Oxford	Birmingham Heartlands Hospital	St Bartholomew's Hospital
Adaptimmune	Standards Coordinating Body	Royal Marsden	Birmingham Children's Hospital	NHSBT (Great Ormond Street Hospital)
Agentus Therapeutics		NHSBT Southampton	Queen Elizabeth Hospital Birmingham	Imperial College Healthcare
Autolus		SNBTS	NHSBT Birmingham Blood Donor Centre	Hammersmith Hospital
Birmingham University		Royal Liverpool University Hospital		King's College Hospital
bluebirdbio		Glasgow	**Blackpool** Blackpool Victoria Hospital	The London Clinic
Cell Medica		Newcastle		Royal Marsden Hospital
Gilead		Cambridge	**Bournemouth and Bristol** Royal Bournemouth and Christchurch	St George's Hospital
GSK		NHSBT Liverpool	Hospitals NHS Foundation Trust	University College Hospital
Cheisi		NHSBT Bristol	NHSBT Filton, Bristol	**Manchester**
Immune Bio		NHSBT Birmingham	**Cambridge**	Manchester Royal Infirmary
Orbson Therapeutics		UCLH	Addenbrooke's Hospital	NHSBT Manchester Therapeutic Apheresis Unit
NHSBT		Nottingham	**Dudley**	The Christie Hospital
Novartis		Cardiff	Russells Hall Hospital	**Newcastle**
Pfizer		The Christie Hospital	**Edinburgh**	Newcastle Freeman Hospital
Reneuron		NHSBT Leeds	SNBTS	Great Northern Children's Hospital
Rexgenero		NHSBT Leeds	**Exeter**	**Norwich** Norfolk and Norwich University Hospital
Roslin Cells		Leicester	Royal Devon and Exeter Hospital	
SNBTS		London Clinic		
TCBiopharma		Great Ormond Street Hospital		
UCL				

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Biovault

Kings

Kings

Glasgow

SNBTS

Leeds

NHSBT

Leicester

Leicester Royal Infirmary

Liverpool

NHSBT

Nottingham

Nottingham City Hospital

Oxford

NHSBT

Plymouth

Derriford Hospital

Poole

Poole Hospital

Sheffield

NHSBT

Sheffield Children's Hospital

Southampton

University Hospital Southampton NHS Foundation Trust

Salisbury District Hospital

Stoke on Trent

Royal Stoke University Hospital

Wales

University Hospital of Wales

Ysbyty Gwynedd, Bangor, North Wales

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2. Collection of Starting Materials

A survey of JACIE accredited apheresis centres in the UK was undertaken with the aim of identifying current practices and to make recommendations for guidance on mononuclear cell (MNC) collection settings and endpoints.

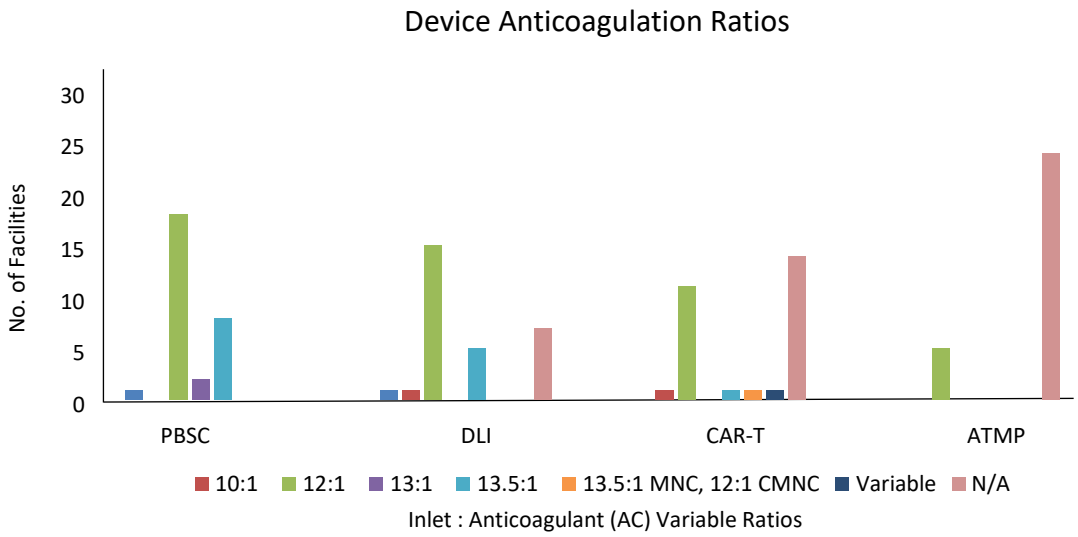

Figure S1. Inlet : Anticoagulation (AC) ratio for all apheresis procedures.

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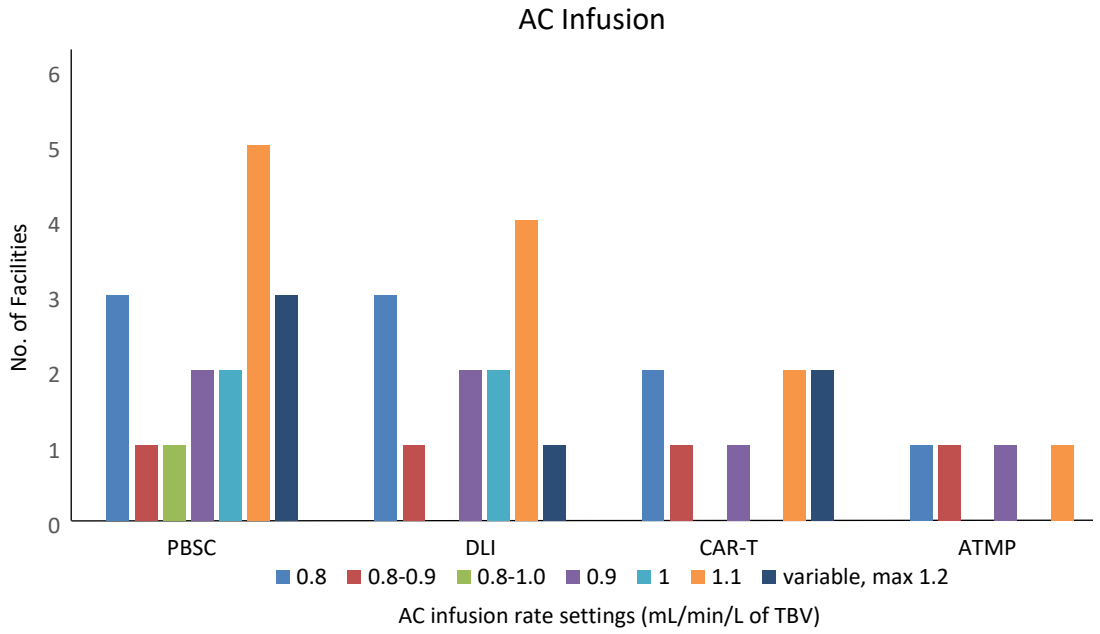

Figure S2. AC infusion rate settings (mL per minute per litre of total blood volume) across all apheresis procedures.

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Table S1. Minimum and Maximum Collection Volumes for CAR-T and other ATMP protocols

Amount of blood processed for the various apheresis collections
(Total Blood Volume [TBV] or Total Amount in Litres [L] as expressed by respondents

Procedure	2 TBV	2.5 TBV	3 TBV	4 TBV	12–15 L	16 L	"Protocol dependent"
PBSC	2	11	7	0	0	1	0
DLI	3	6	3	0	1	1	0
CAR-T	1	4	1	0	2	0	2
ATMP	1	3	0	1	1	0	1

Minimum volumes processed in various apheresis collections
(Total Blood Volume [TBV] or Total Amount in Millilitres [mL] as expressed by respondents)

Procedure	Volume	Number of respondents
PBSC	40 mL	1
	60 mL	1
	2 TBV	1
	2.5 TBV	1
	None	24
DLI	60 mL	1
	80 mL	1
	100 mL	1
	2.5 TBV	1
	None	11

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	N/A	11
Lymphocytes for CAR-T	40 mL	1
	None	5
	N/A	20
Mononuclear cells for ATMPs	50 mL	1
	None	2
	N/A	22

Maximum volumes processed in various apheresis collections
(in Total Blood Volume [TBV] and Total Amount in Millilitres [mL], as expressed by respondents)

Procedure	Volume	Number of respondents
PBSC	300 ml	2
	350 ml	1
	2.5 TBV	2
	3 TBV	1
	None	11
	N/A	7
DLI	150 ml	1
	280 ml	1
	300ml	1

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	2.5 TBV	1
	None	9
	N/A	9
Lymphocytes for CAR-T	2.5 TBV	1
	None	6
	N/A	15
Mononuclear cells for ATMP	100ml	1
	2.5 TBV	1
	None	2
	N/A	17

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Advanced Therapy Treatment Centres

Figure S3(a-c)

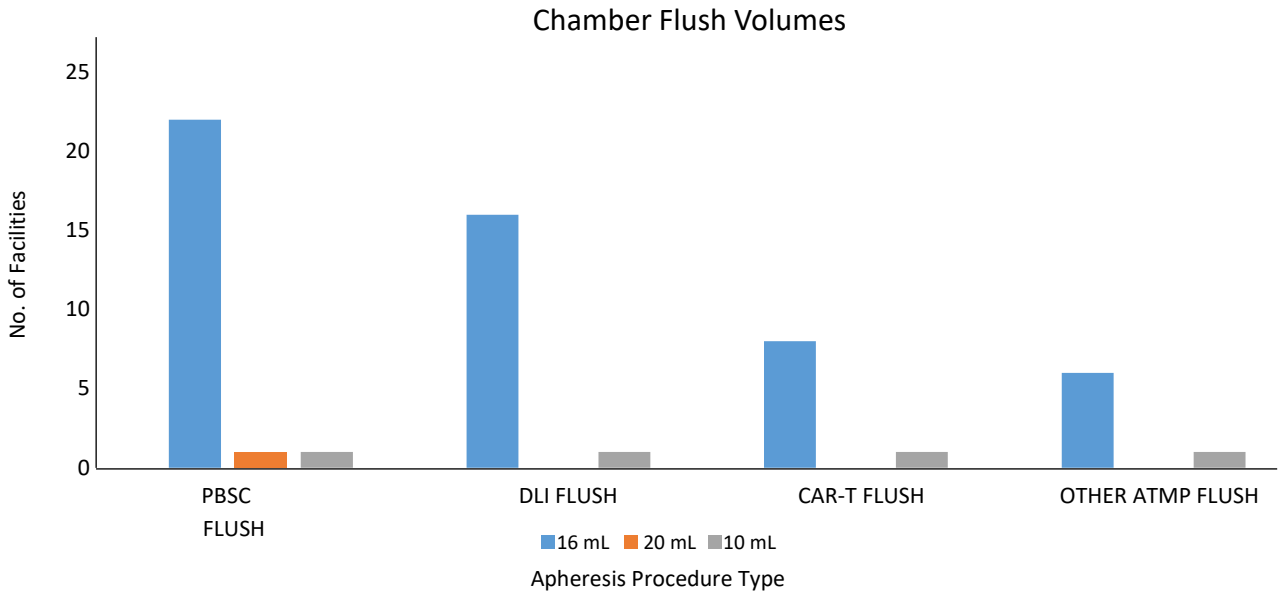

Figure S3(a). Chamber Flush Volumes with MNC Programme Across Apheresis Procedures.

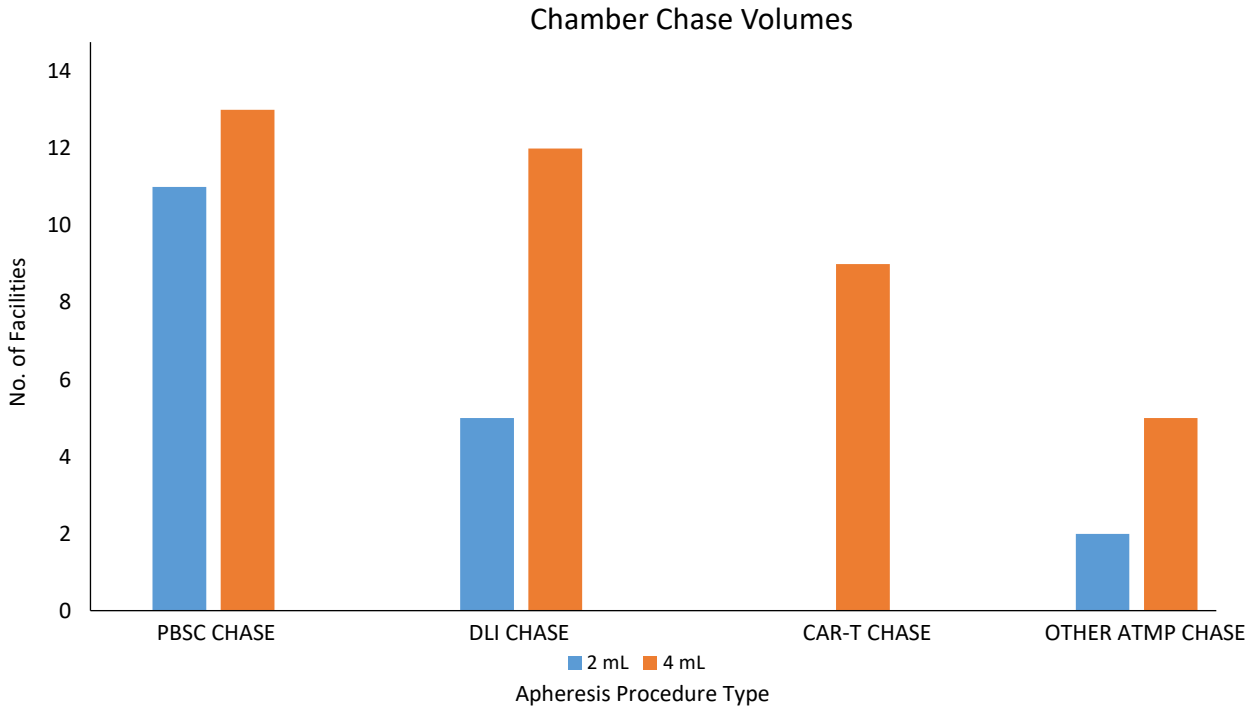

Figure S3(b). Chamber Chase Volumes with MNC Programme Across Apheresis Procedures.

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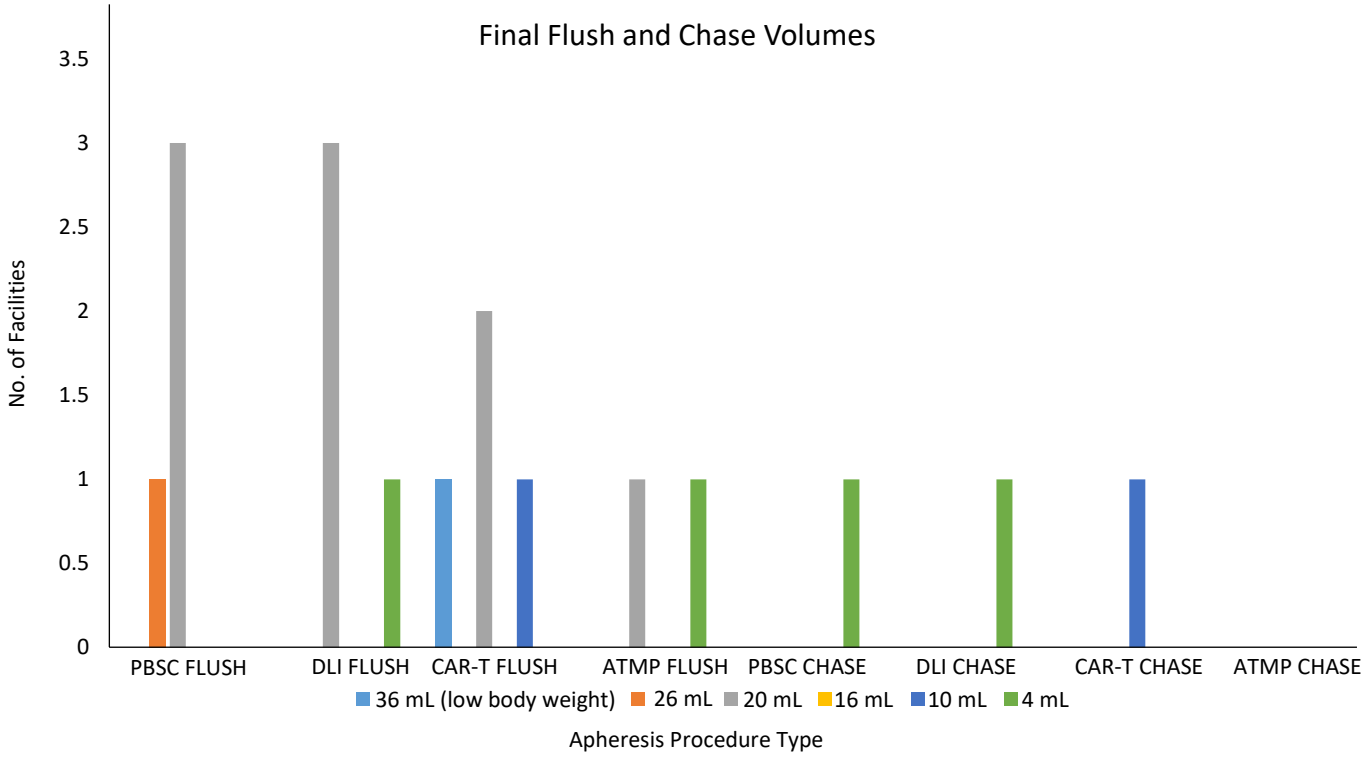

Figure S3(c). Final Flush and Chase Volumes with MNC Programme Across Apheresis Procedures.

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Table S2. Patient, procedure and collection efficiency data

Procedure Data	Respondence, n (%)
Pre-procedure data collected	
Diagnosis	28 (100)
White cell count	28 (100)
Weight	28 (100)
Total blood volume	27 (96)
Platelet count	27 (96)
White cell differential	16 (57)
Haematocrit	27 (96)
CD34 (PBSC)	28 (100)
CD (Lymphocytes for CAR-Ts)	11 (39)
Other CD counts	1 (3.5)
None of the above	0 (0)
Post-procedure data collected	
White cell count	11 (39)
White cell differential	7 (25)

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Product CD34 count (PBSC)	18 (64)
Product CD3 count (T lymphocytes)	8 (28.5)
Other CD counts	0 (0)
Product TNC	10 (35)
Product volume	27 (96)
Product platelet count	6 (21)
Product haematocrit	6 (21)
None of the above	11 (39)
Post-procedure patient/donor information collected	
White cell count	16 (57)
Haematocrit	15 (53.5)
White cell differential	10 (35)
CD34 post count	10 (35)
CD3 post count	10 (35)
Other CD counts	0 (0)
None of the above	11 (39)

Abbreviations: CAR-T, chimeric antigen receptor T-cell therapy; CD, cluster of differentiation; n, number of respondents; PBSC, peripheral blood stem cell; TNC, total nucleated cell.

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12. Acknowledgements

12.1 Working Group Members and Affiliated Organisations

Name	Organisation	Name	Organisation
Bill Shingleton	Cytiva	Jennifer Armstrong	Terumo
Chris Fong	Autolus Limited	Jo Tomlins	The Christie NHS Foundation Trust
Claire Brady	Cell and Gene Therapy Catapult	Joy Sinclair	bluebird bio
Davina Potok	NHS Blood and Transplant	Julie Guest	Great Northern Children's Hospital
Di Sweeny	The Christie NHS Foundation Trust	Justina Chuku	Cell and Gene Therapy Catapult
Dominic Reeks	GlaxoSmithKline plc	Lynn Manson	Scottish National Blood Transfusion Service
Doreen Condon	bluebird bio	Marc Turner	Scottish National Blood Transfusion Service
Douglas Watson	Novartis	Maria Kerr	NHS Blood and Transplant
Drew Hope	Autolus Limited	Natalie Francis –	GlaxoSmithKline plc
Elia Piccinini	Kite Pharma	Neil Bell	Autolus Limited
Haili Cui	Kings College Hospital NHS Foundation Trust	Pauline Johnstone	Autolus Limited
Helen Delahaye	Autolus Limited	Richard Smith	Be The Match
Helen Keane	University College London Hospital NHS Foundation Trust	Rita Angelica	The Christie NHS Foundation Trust
Jacqueline Barry	Cell and Gene Therapy Catapult	Wendy Ogden	Manchester NHS Foundation Trust
James Griffin	NHS Blood and Transplant	Will Shingler	Autolus Limited

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12.2 Organisations that reviewed or provided feedback

Adaptimmune Therapeutics plc	Kite Pharma
Autolus Limited	NHS Blood and Transplant
Be the Match	Novartis
Cell and Gene Therapy Catapult	Scottish National Blood Transfusion Service
Imperial College Healthcare NHS Trust	TC BioPharm Limited
INmuneBio	The Christie NHS Foundation Trust

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