Apheresis Collection of Starting Material for ATMP Manufacture
Exemplar Process Flow, Challenges and Solutions

Background

Advanced Therapy Medicinal Products (ATMPs) must be safe, effective and of a high quality when administered to the patient. To achieve this, the activities carried out at each stage of the ATMP supply chain must be controlled and standardised wherever possible to ensure safety of the end product, simplification of the process and so reduction in the risk of errors, while also meeting all regulatory and accreditation requirements.

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 from the patients themselves, biological variability between and within donors will affect the quality of the cells collected. Patient-related factors of relevance will be the patient's underlying diagnosis, past and current treatment and current health. Also, interaction with ATMP manufacturers whose processes are managed within different regulatory frameworks to those of the clinical apheresis units may result in unwarranted change to the collection process through lack of understanding of acceptable similarities and differences between organisational regulatory and accreditation requirements.

There is limited capability to control patient- and donor-related factors that could impact on the quality of the 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 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 – for example, in the European Union under the Tissues and Cells Directives (2004/32/EC) as transposed into Member State law. Professional accreditation bodies' standards such as the FACT-JACIE International Standards for Haematopoietic Cellular Therapy Product Collection also play a role within the clinical apheresis unit in ensuring collections are carried out in a controlled and safe environment.

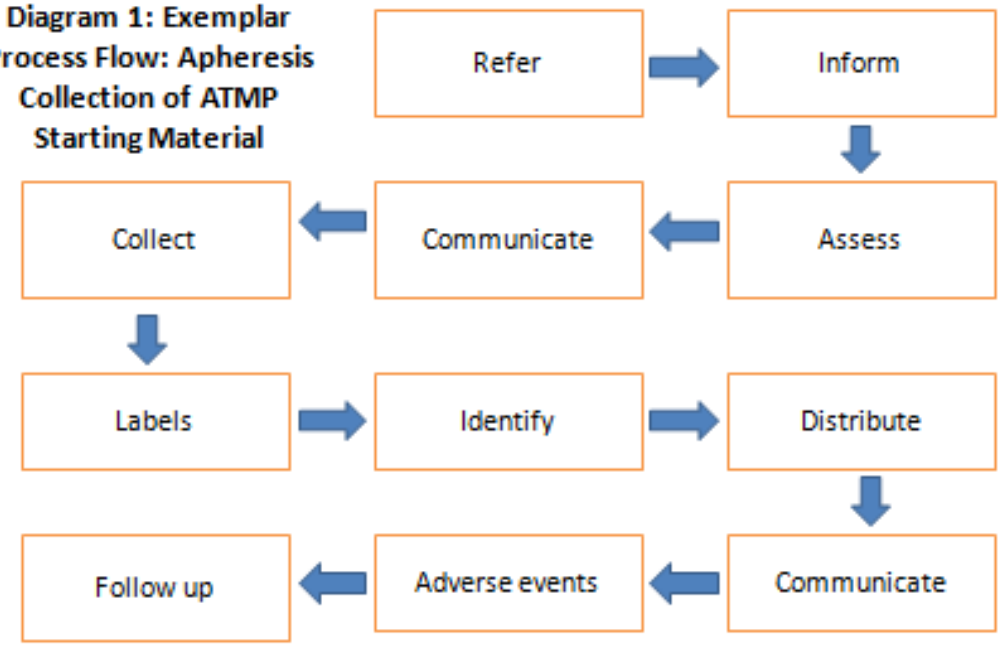
An exemplar process flow for the apheresis collection of ATMP starting material is described (Diagram1), areas of challenge and uncertainty highlighted and possible solutions suggested. The foundation for collection process control should be the FACT-JACIE collection standards as apheresis collection of haematopoietic cells for ATMP manufacture falls within scope of this accreditation framework. 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 outwith the jurisdiction of the facility may apply; for example, when a facility is sending cellular therapy products outwith its immediate jurisdiction. 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).

For the purpose of this guideline, both autologous (i.e. patients) and allogeneic donors (related and unrelated) can undergo collection of ATMP starting material and the requirements apply to both adults and children in each subcategory. Collections can be carried out as part of the patient's standard management plan or within a clinical trial or as an elective donation by a healthy donor for manufacture of an allogeneic product.

Diagram 1: Exemplar Process Flow: Apheresis Collection of ATMP Starting Material



Explanatory Notes

Refer *patient /donor from the clinical or donor team to the collection facility*: 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 patient's /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. Unique patient /donor identifiers should be given.

Inform, *counsel and consent the patient or donor on the collection process*: these activities may be done by the clinical or donor team before referral of the patient /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 patient / donor in advance of the face-to-face assessment, and any questions arising from the leaflet's 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 patient / donor and use language and terminology that can understood by the patient / donor. If there are communication challenges, these must be overcome to ensure that the patient /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 patient with incapacity who has been referred for collection must be met.

Assess *the suitability of the patient / donor to undergo the collection process*: these activities may be done by the clinical or donor team before referral of the patient / 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 patient's / donor's health and wellbeing are not compromised by undergoing the collection process. The patient's / donor's eligibility to donate must also be determined to ensure that the risk of infection or other disease transmission 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 infectious, autoimmune or neoplastic disease does not apply. 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 patient, local donor acceptance criteria can be consulted and a specialist opinion sought.

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. 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) within 30 days of 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.

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 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 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 use of the ineligible donor, a documented protocol exception can be considered subject to a risk assessment on a case-by-case basis.

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 patient / donor is suitable and eligible to undergo collection. The extent of information that relates to the patient's / 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. This 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.

Patient / donor undergoes ***collect****ion*: the patient / 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 memoire format to reduce the likelihood of errors being made in the collection process. Staff must be trained against the aide memoire document to ensure that each ATMP manufacturer's collection requirements are met. The more standardised these protocols are the less the duplication of work and risk of error.

In the UK, ATMP collections can be made under 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 HTA licence which is consistent with EU Tissues and Cells Directive (EUTCD) requirements.

The EUTCD refers specifically to testing requirements when collecting haematopoietic progenitor cells for stem cell transplantation. For autologous donors (i.e. patients) this includes mandatory infection marker testing within 30 days of collection and no requirement for testing immediately prior to collection (on the collection day). However, when a patient undergoes collection of the starting material for ATMP manufacture, the UK Competent Authority does not permit omission of day of collection mandatory infection marker testing as the cells are not going to be used for stem cell transplantation.

It must be determined in advance of the collection whether or not the results of 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 that 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 patient / donor and product identification*: patient / donor-identifiable data must be placed on the collection bag label and the accuracy of the data verified before the bag is removed from the immediate vicinity of the patient /donor to ensure that the cells in the bag have originated from the patient /donor named on the bag. Label product identification data must be compliant with current terms and definitions related to cellular therapy using either ISBT 128 or Eurocode standard terminology, and include the alphanumeric identifier consistent with the Single European Code legislation (SEC-donor identification sequence). Hand-written data must be written in indelible ink that will not smudge during distribution and on receipt by the ATMP manufacturer.

*At a minimum, a unique **identifier** must remain on the cellular therapy product label at the point of distribution to the ATMP manufacturer if patient /donor identifiable data has been obliterated prior to distribution*: the general principle of the data protection regulations in the UK is to minimise sharing of data collected from European Union individuals, 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 is outwith the collection facility's control, it may be used by the ATMP manufacturer and this carries with it a reputational risk for the collection facility if data is shared with individuals within the ATMP manufacturer who do not need to have access to it.

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 PII that must remain visible on the collection bag label and accompanying documentation, and all unnecessary data must be obliterated. 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 obliterated. If the patient's / donor's starting material has been collected as part of a clinical trial, this may be the unique study number. A process must be in place whereby the unique identifier can be associated with the patient / donor from the point of distribution from the collection facility through all steps of manufacturing to infusion into the patient.

*The cellular therapy product leaves the control of the collection facility and is **distribute**d*: 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. A validated distribution box must be used and it must be agreed in advance between the collection/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 product distribution process must be explicitly set out in the contractual agreement between the collection / 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 being met will lie with the ATMP manufacturer.

Storage within the collection facility occurs from the end of the collection procedure until the cellular therapy product leaves the control of the collection facility. Short- and longer-term storage conditions must be defined and actions to take if storage conditions fall outwith specification determined.

There must be documentation of the cellular therapy product leaving the control of the collection facility and being handed over into the control of the processing facility and thereafter to the courier (or directly from the collection facility to the courier). The collection/ processing facility staff and the courier must sign against their activity in the handover process, and the collection/processing facility staff must confirm that the cellular therapy product has met pre-determined release criteria. If it has not, the cellular therapy product may be released by exception so long as an urgent medical need is justified and documented.

The documented handover of the cellular therapy product 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 confirm with all relevant data protection regulations; UK data protection regulations apply in the US if the data source originates within Europe. The collection / processing facility and ATMP manufacturer must agree in advance the extent of PII that must accompany the collection at distribution.

*A collection episode summary is **communicate**d to the referring team, family doctor and ATMP manufacturer*: details relating to the collection episode, including any side effects experienced by the patient / donor whilst undergoing collection, should be forwarded to the referring team, the patient's / donor's family doctor and the ATMP manufacturer or local processing facility (as applicable). Information on whether or not 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 Competent Authority of any serious adverse events or reactions occurring during the collection episode, as required by the EUTCD. Details must be shared with the referring team if the patient / donor has undergone collection as part of a clinical trial.

*The patient / 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 patient / donor to ensure that they have not experienced any untoward side effects attributable to the collection episode and 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 routine review process.

Table 1: Regulatory, Accreditation and Guidelines Frameworks

Process	Organisation	Guidance Document	Voluntary or Mandated Compliance
Collection	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, and Administration www.jacie.org	Voluntary
	HTA (Human Tissue Authority)	EU Directives 2004/23/EC, 2006/17/EC and 2006/86/EC; Human Tissue (Quality and Safety for Human Allocation) Regulation 2007	Mandatory
		HTA Codes A (Consent), E (Research), G (Allogeneic Bone Marrow and Peripheral Blood Stem Cell Donation)	Mandatory
		Montgomery v Lanarkshire Health Board [2015]UKSC 11 (11 March 2015)	Mandatory
		Mental Capacity Act (2005) Adults with Incapacity (Scotland) Act 2000	Mandatory
Labelling & Coding		ISBT 128 using ICCBBA Standard Terminology for Blood, Cellular Therapy, and Tissue Product Descriptions www.iccbba.org	Mandatory
		Eurocode-BLS www.eurocode.org	Mandatory
		SEC: Commission Directive (EU) 2015/565 amending Directive 2006/86/EC (published April 9 2015)	Mandatory
Data Protection	OIC	General Data Protection Regulation (GDPR) Regulation (EU) 2016/679 Data Protection Act 2018	Mandatory

	(Office of the Information Commissioner)		
Donor Selection	HTA	Bone Marrow and Peripheral Blood Stem Cell Donor Selection Guidelines for Unrelated Donors (Haematopoietic Progenitor Cells), Guidelines for the Blood Transfusion Services in the United Kingdom	Mandatory
		Geographical Disease Risk Index, (Haematopoietic Progenitor Cells), Guidelines for the Blood Transfusion Services in the United Kingdom www.transfusionguidelines.org	Mandatory