Advanced Therapy Treatment Centres	**Guidance:** ATiMP Clinical Trial Quality Technical Agreements				
Document Number:	**IAG.27**	**Version**	**1.0**	**Dated**	**6th December 2021**
Related IAG WG:	**IAG Clinical Trials**			**Related Outputs:**	**IAG/CT/O2**

1. Quality Technical Agreements (QTAs)

This guidance document provides an oversight of the purpose and contents of a Quality Technical Agreement (QTA) for use between clinical trial Sponsors and Participating Organisations (i.e., research sites) within the UK. This resource is intended to be used as a reference document, with the aim of reducing variation across QTAs in use across the UK. It is not a template agreement.

An effective QTA serves a key purpose for advanced therapy medicinal product (ATMP) research, outlining the roles and responsibilities of the parties involved in the supply of human cells and associated drug product for a trial. It is not simply an administrative exercise and should be approached with careful thought. This guidance contains practical information to consider when implementing a QTA within the UK healthcare system.

The QTA is one part of a suite of documentation and agreements that are used in the management of ATMP trials. Therefore, it is important for both the Sponsor and Participating Organisation to be clear on the particular function of the QTA for a specific trial. For instance, are there service-level agreements with third parties to consider? What information concerning the management of human cells and study product are outlined in the trial protocol? It is also vital to understand the processes and procedures contained within each organisation's Quality Management System (QMS) to ensure the QTA does not contradict any local procedures, avoid any unnecessary duplication, and ensure that the content of the QTA can be implemented appropriately. For some sponsors, it may be more convenient to include the QTA as a schedule to a clinical trial agreement for a project instead of a standalone agreement.

The competent authority for The Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) (regulations that impose safety and quality requirements in relation to human tissue and cells intended for human application) is the Human Tissue Authority (HTA). Activities related to the starting material for ATMP manufacture, such as procurement (including consent and donor selection) and donor serological testing must be undertaken under the oversight of an establishment holding a suitable HTA-issued licence. In some cases, initial processing and/or storage activities may also fall within the scope of HTA-licensing requirements. Clinical trial authorisations for ATMPs, and manufacturing/import of ATMPs, are overseen by the Medicines and Healthcare products Regulatory Agency (MHRA), as the applicable competent authority. Stakeholders are advised to contact the relevant authorities for any queries concerning licensing requirements.

The HTA/MHRA do not prescribe what should/should not be contained in a specific QTA or mandate the format of the agreement provided minimum requirements are met. The HTA have provided a Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment (https://www.hta.gov.uk/guidance-professionals/regulated-sectors/human-application/hta-guide-quality-and-safety-assurance - accessed Aug 2021) which contains extensive detail on the management of human cells relevant to ATMP trials and the content of associated agreements (including export and import requirements) that should be considered when creating/implementing a QTA.

Practically, it is important for the Sponsor to route the agreement through the correct department/role at the Participating Organisation. It is unlikely that the standard contracting functions at an NHS site (including Trust Legal Services [or equivalent] and Research and Development contracting teams) will have the specialist knowledge of the applicable legislation, regulation, and guidance to review and agree a QTA. Many organisations who are active in ATMP research will have a specific individual who is responsible for QTAs as part of the role (often this is an organisation's Designated Individual [DI]). The Participating

Organisation's Clinical Trial Pharmacy will also be a key stakeholder in the review/execution of a QTA for ATMP trials. It is important to ensure that activities undertaken under the authority of a stakeholder's licence(s) are incorporated within the licence's governance systems and the oversight of key staff working under the licence, such as the DI of the HTA licence.

There is an expectation that a QTA will include timelines for notifications of changes to the agreement. This can be included in an appendix within the QTA.

2. Roles and responsibilities

A typical QTA for a trial will document the roles and responsibilities assigned to each party involved in the supply of human cells and finished product for the study. A 'checklist' within the QTA is a straightforward way to display roles and responsibilities. This is most easily undertaken by using a simple table format, as per the example shown below (Table 1).

The level of detail contained in a QTA concerning processes to be followed, and the associated oversight mechanisms, should be considered on a trial-by-trial basis. Parties would be expected to be able to demonstrate how roles and responsibilities assigned in the QTA have been implemented effectively if inspected; where the QTA does not contain specific details concerning how roles and responsibilities will be undertaken, parties would be expected to demonstrate that this detail is provided in other appropriate documentation instead (for e.g., SOPs, separate agreements) and that effective signposting to this information is included within the agreement.

Table 1, below, provides an outline of a suggested layout for the Roles and Responsibilities section of a QTA. When using a table format, it can be helpful to enter the categories in the order that activities will occur for the trial if practical, as this can add context.

Table 1:

Item/ ref #	Responsibility/requirement	Supporting information / details	Sponsor	Participating Organisation / clinical site	N/A
1.	Category 1				
1.1.	*Add specific responsibility*	Supporting information, including reference links where appropriate/required.	✓	✓	
1.2.	*Add specific responsibility*				
1.3.	*Add specific responsibility*				
2.	Category 2				
2.1.	*Add specific responsibility*				
2.2.	*Add specific responsibility*				

2.1. Example roles and responsibilities

Table 2 contains an overview of roles and responsibilities that may be assigned as part of a trial. Although this list is non-exhaustive, it is extensive. Not all responsibilities may be applicable to each trial. Suggested roles/responsibilities have been assigned to provide an indication of a typical agreement between Sponsors and Participating Organisations, however this should always be carefully considered on a trial-by-trial basis to ensure compliance with the study protocol and other trial agreements, and the QMS of each organisation.

It is important that a QTA is not unnecessarily overly detailed and/or prescriptive to the point of restricting proper process and the functionality of the organisations involved, because ultimately this may become unworkable and can cause avoidable compliance issues for the parties involved. Instead, a proportionate approach should be followed, ensuring that all necessary regulatory and process concerns are addressed effectively while retaining the necessary flexibility for both parties to deliver the trial.

Table 2:

Suggested category	Suggested/ likely responsible party	Example responsibilities and guidance/background information
Compliance	Both	• Licensable activities must be undertaken under the authority of an appropriate licence issued by the relevant national authority (for the UK, this would be the HTA and/or MHRA, depending on the involvement of the Participating Organisation in either the procurement of materials and donor testing or the subsequent manufacturing processes [or both, if applicable]). The clinical site must be in possession of a valid licence for their activities/the activities to be undertaken as part of the research (unless their activity is covered under a tri-partite agreement with another site which holds the licence). • Sponsor organisation may also require/prefer the Participating Organisation to be JACIE accredited, and should specify if this is desired/ essential (JACIE: Joint Accreditation Committee International Society Cell and Gene Therapy [ISCT] -Europe & European Society for Blood and Bone Marrow Transplantation [EBMT] https://www.ebmt.org/jacie-accreditation). • Sponsor may stipulate that the participant organisation should inform the Sponsor if there are amendments to licensing/accreditation, either as part of this responsibility or as a separate line.
	Participating Organisation	Sites must comply with all applicable regulations and all applicable internal procedures for sample(s)/products(s) collection, starting material processing and storage (if applicable), labelling, packaging and shipment to and receipt from the Manufacturing Site. • Sponsor may specify the particular regulations that are applicable, which can include: - EU Directives: - 2002/98/EC - 2004/23/EC - 2006/17/EC (amended by 2012/39/EU) - 2006/86/EC (amended by (EU) 2015/565) - (EU) 2015/566. - Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended) - Human Tissue Act (2004) • This may also stipulate compliance with all study-specific procedures as per study documentation. Alternatively, this could be added as separate responsibility.
	Sponsor	The Sponsor must be in possession of an applicable Clinical Trial Authorisation issued by the relevant competent authority for the duration of the Study. For the UK the competent authority is the MHRA.
	Participating Organisation and/or Sponsor	Sponsor and Participating Organisation(s) must comply with Good Clinical Practice (GCP).
	Sponsor	The Sponsor organisation will provide trial documentation, including but not limited to a Clinical Trial Protocol, and manuals for Apheresis, Infusion, Drug product, as applicable
	Participating Organisation.	Ensure all documentation is completed and the documentation procedures (detailed in documents such as the Clinical Protocol, Apheresis Manual and Drug Product and Infusion Manual, as applicable) are followed.
Participant procedures /	Sponsor	The informed consent form(s) (ICF) will be provided by the Sponsor and localised by the site. ICF(s) will be REC approved.

Suggested category	Suggested/ likely responsible party	Example responsibilities and guidance/background information
sample collection / procurement	Participating Organisation.	Consent should be obtained by an appropriately trained member of staff, specifically the Principal Investigator conducting the Study or a person who is named on the delegation of responsibilities log of the study and who has been appropriately trained (as per the UK Clinical Trial Regulations 2004, as amended). Consent must be obtained in accordance with the requirements of the Human Tissue (Quality and Safety for Human Application) Regulations 2007 (as amended). If required (for e.g., because this is not covered in other QMS documentation) it may be necessary to stipulate further considerations, including that consent includes testing for infectious diseases, for access to medical records, traceability, right of withdrawal etc. however this is often already covered in existing trial/site documentation. Sites will also be responsible for ensuring that participant eligibility criteria have been met prior to entry into a trial. Procurement of samples must be undertaken in accordance with the regulatory requirements outlined above, and with the Sponsor's trial documentation. The QTA and/or trial documentation must specify the requirements and parameters applicable to procurement (for e.g., minimum cell counts, processing requirements). Where processing is undertaken under a HTA licence, an authorised Preparation Processing Document (PPD) may be required (if one is not already held by the Participant Organisation in question).
	Participating Organisation.	Sites will ensure that participants are tested and resulted negative (unless otherwise stipulated in the case of autologous procurement only) for infectious diseases and will verify and communicate the test results as per the study documentation. If specific details for this process are not included in the QTA signposting to other documentation should be made available. In the UK, this is a licensable activity (HTA licence). Minimum regulatory requirements for the tests to be undertaken and timing of collection of the serological sample are described in the HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment.
	Participating Organisation and/or Sponsor	The QTA may specify responsibilities concerning the process of sample collection and associated traceability requirements, which may be attributed to Sponsor and/or Participating Organisation. This may include: • Provision of the collection kit(s) for tissues/cells, and/or specification of the types that should be used for the trial. • Collecting patient materials according to the associated clinical trial documentation and as per approved procedures. • Maintaining appropriate chain of custody documentation/evidence (e.g., ensuring identity is maintained for samples/product) as per all applicable regulations. For apheresis processes, guidance can be found in the 'UK review and recommendations on the procurement of starting materials by apheresis for advanced therapy medicinal product (ATMP) manufacture' document published by the Advanced Therapy Treatment Centres (ATTC) Network – accessed September 2021.
Quality management	Participating Organisation and/or Sponsor	It is likely that specific requirements such as traceability, record keeping and control measures are documented in an organisation's QMS, and it would therefore not be necessary to duplicate that info here if all applicable requirements are met. Instead, the QTA can contain responsibilities (for both parties) to maintain their QMS to the standards required by regulation and guidance, and to agree to always comply with them.

Suggested category	Suggested/ likely responsible party	Example responsibilities and guidance/background information
		The QTA can document quality complaint handling and/or recall procedures between Sponsor and Participating Organisation if required. It may also outline termination criteria (i.e., conditions that if met would void the agreement, such as the revocation of a required licence at an organisation).
Training / study personnel	Participating Organisation.	Sites must ensure the required number of trained individuals are available to perform and supervise the procurement, testing and release of patient materials for the trial, as specified by the Sponsor
	Participating Organisation.	Sites will ensure individuals have appropriate training, education/qualification and/or experience to perform their assigned duties/roles, and that this is documented in training records. This should include for participant/donor identification and consent purposes.
Drug product manufacture and administration	Sponsor	The Sponsor will take responsibility for ensuring that the manufacturing process is conducted by a suitable manufacturing organisation (whether that is in-house or outsourced to a third-party organisation) that operates within Good Manufacturing Practice (GMP), relevant laws and applicable regulations.
	Participating Organisation.	Participating Organisation responsibilities for receipt of the drug should include ensuring appropriate drug storage in compliance with the drug label and maintaining those agreed storage conditions. Administration will be as per the study protocol and associated approved documentation.
Audit and inspection	Both.	Evidence that agreed responsibilities have been met if required/requested by regulatory, governmental body and/or a party to this agreement.
	Participating Organisation and/or Sponsor	Activities must fall within a licence's governance systems, including the audit program. Therefore, for the purposes of the QTA audit requirements will depend largely on the internal processes of the parties to the QTA. It may be desirable to include only general items regarding audit and follow-up actions (for e.g., 'an audit will be performed periodically, with ___ hours/days' notice'). It would also be acceptable to add a more specific series of responsibilities with additional detail about scheduling, reporting, corrective actions etc. and respective timelines, if this is not already stipulated in parties internal processes/trial documentation/other agreements. Agreements should include a clause ensuring the relevant authority the right to inspect activities should it wish to do so.
Shipping, handling, storage	Participating Organisation and/or Sponsor	The Sponsor will define the storage and handling requirements for products; this may be separated into starting material products and IMP products, recognising that the responsibilities for each may differ. It may be preferential to include these in detail in the QTA, or to refer to separate QMS or study-specific documentation. Site responsibilities include ensuring activities are undertaken in accordance with regulatory and Sponsor requirements, as set out in agreements and associated documentation, maintaining procedures to ensure control (access and environmental) of storage areas, verifying package integrity and compliance of documentation/labelling prior to shipment and to ship samples/products as per agreed processes and with applicable documentation. Specific responsibilities of the parties may include: • Validation that shipping conditions have been met upon receipt. Retaining records of shipments, including temperature monitoring recordings. • Arranging/liaison of collection

Suggested category	Suggested/ likely responsible party	Example responsibilities and guidance/background information
		• Agreement(s) with a courier(s). Of particular importance is the process for maintaining oversight of the transport process and which party takes responsibility for this (for e.g., if the Sponsor is contracting directly with a courier, how will the Sponsor maintain effective oversight of the conduct of the courier when collecting/delivering to the Participating Organisation? How would the Participating Organisation be informed if there is an issue with the transport of samples collected at the site? How would a Participating Organisation inform the Sponsor of excursions from the agreed process? Who will adverse events during transport be reported to ensure onward reporting to the appropriate regulatory authority?). If this is addressed in accompanying documentation it should be clear where, and the QTA must be worded such that parties are required to abide by any referenced associated documents. The HTA guide referenced above specifies the minimum requirements for agreements. The participant organisation should have the opportunity to review/audit the processes and agreements in place between a Sponsor and a courier. The courier must be able to evidence that they are able to transport the study-specific samples/products. • Distributor compliance with Good Distribution Practice (GDP), as regulated by the MHRA. Following agreed processes and standards for packing materials.
Import and export	Sponsor	For the import of tissue, extensive guidance is available from the HTA (HTA guide to Quality and Safety, as referenced above). Specifically, sections 254 and 255 of the Guide covers in detail the requirements for an Importing Tissue Establishment (ITE) that are required to be evidenced and followed. Export responsibilities are less specific in the Guide and relate to ensuring oversight on the export process (couriers, handovers, times, documentation etc.). The HTA would expect that an organisation responsible for export will have procedures in place to ensure that only material that is compliant with applicable regulations, legislation and guidance is exported. If the Sponsor will be importing/exporting tissue as part of the trial, then these responsibilities can be made clear in the QTA. Suitable licence authorisations must be in place.
Change controls and oversight	Participating Organisation and/or Sponsor	The Sponsor organisation may want to be notified of/give permission for any changes to the Participating Organisation's facilities/equipment/processes etc. that would impact upon the Participating Organisation's agreed functions. This should be worded carefully to ensure that the burden on the Participating Organisation is realistic/deliverable and that a pragmatic approach is followed (for e.g., a Participating Organisation with a portfolio of trials may not realistically be able to provide change requests to a cohort of Sponsors every time an amendment is made to how the site functions, as this would adversely affect delivery).
Testing (any testing within ATMP pathway; ensure specifics are referenced where required)	Participating Organisation and/or Sponsor	Testing responsibilities may fall to either the Participating Organisation or the Sponsor (often dependent on Sponsor-specific processes as per their QMS). The QTA should make clear which organisation is responsible for testing, the timing of sample collection for mandatory serological testing, how results will be shared, reporting for positive results etc. Donor serological testing must be undertaken under the authority of a suitable licence
Labelling of procured product	Participating Organisation and/or Sponsor	The QTA can provide details of the labelling requirements for the study. These may be defined in the study manual(s), or simply refer to regulatory and JACIE/ISBT128 standards, which are widely used and accepted, and can help to reduce variation between trials for Participating Organisations

Suggested category	Suggested/ likely responsible party	Example responsibilities and guidance/background information
		(and reduce discrepancy in process between routine care and trial sample/product management).
Non-conformance and safety reporting	Participating Organisation and/or Sponsor	Responsibilities for Serious Adverse Event (SAE)/ adverse reaction (AR) and non-conformance processes (for e.g., communication timelines between Sponsor and site, notification of the competent authority, record keeping) are likely covered in the study protocol, organisation's QMS and/or the study clinical trial agreement. Responsibilities for reporting of SAE/ARs that may relate to the quality or safety of tissues/cells should be included in agreements between the parties and conform to the requirements set out in paragraph 217 of the Guide.
Sub-contractor	Participating Organisation and/or Sponsor	Either the Sponsor or Participating Organisation may use a sub-contracted organisation for sample/product related duties (for e.g., manufacturing, central apheresis lab). The QTA may specify the oversight responsibilities of that organisation to their sub-contractor, and/or the access of the other party to review those arrangements. Suitable agreements must be in place with sub-contractors. Where sub-contractors undertake licensable activities on behalf of an HTA-licensed establishment, regulatory requirements for third parties and third-party agreements, as set out in the above-referenced HTA guide, must be met.
Returns/Disposal	Participating Organisation and/or Sponsor	Return and/or disposal responsibilities for waste tissue or unused product may be applicable to either organisation, depending on the processes involved in the collection of samples and manufacture of product. For e.g., this may include instructions for the return/disposal of product transported to site for a patient who is subsequently unable to be dosed.