Specialist Pharmacy Service

National Pharmacy Clinical Trials Advisory Group

Costing Clinical Trials of Advanced Therapy Investigational Medicinal Products using the NIHR interactive Costing Tool – Advice for Pharmacy Sites

Pan UK Pharmacy Working Group for ATMPs

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The Pan UK Pharmacy Working Group (PWG) for Advanced Therapy Medicinal Products (ATMPs) acts as an expert and informed body to support the activities of UK Pharmacies to facilitate ATMP usage. The group consists of pharmacists from across the UK that specialise in the governance, prescribing, administration and monitoring of ATMPs. The aims of the group are to promote good practice, identify and resolve pharmacy issues to maximise the effectiveness and development of services for hospitals to administer advanced therapies. The Pan UK PWG for ATMPs has a clinical trials subgroup which identified a need for guidance when costing trials involving ATIMPs.

This guidance has been ratified by the National Pharmacy Clinical Trials Advisory Group.

The lead authors would like to thank all who have contributed to the production of this guidance, including Clinical Trials subgroup members of the Pan UK PWG for ATMPs, NPCTAG reviewers and members of the NIHR ATMP Costing Working Group.

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Costing Clinical Trials of Advanced Therapy Investigational Medicinal Products (ATIMPs) using the interactive Costing Tool (iCT): Pharmacy Considerations and Guidance for NHS Sites and Commercial Sponsors.

Background

The National Institute for Health and Care Research (NIHR) Industry Costing Template (secondary care) was developed for transparent cost calculation to support budget negotiations for commercial contract clinical research. In 2020, a number of activities related to advanced therapies were added to accommodate the delivery of clinical research involving Advanced Therapy Investigational Medicinal Products (ATIMPs).

In April 2021, the NIHR launched a fully web-based interactive Costing Tool (iCT) within the NIHR Central Portfolio Management System (CPMS); the aim of a digital platform to enable quicker costing and contracting between site and sponsor.

All tariffs were transferred across to the iCT and incorporate:

- NIHR 2021 Investigation and Intervention Tariff
- NIHR Departmental, Set Up and Closedown Tariff 2021-22
- NIHR Procedures Definitions and Tariff 2021-22
- NHSE Market Forces Factor 2021-22

The current hourly rate for pharmacy activity within the iCT is based on the Agenda for Change Band 7 rate (currently expressed as the Manager/nursing rate).

As experience with ATIMP trials has increased over the years, it is acknowledged, both by industry and NHS partners, that increased transparency in resource requirements and associated costs for ATIMP trials is required. Notably, as ATIMP activities may not always fall discretely within pharmacy, or occasionally, even within the same organisation, delivery could vary considerably from trial to trial. Activity and resource requirements may therefore differ substantially from the more traditional pharmacy activities. On this basis, the Clinical Trials subgroup of the Pan UK Pharmacy Working Group (PWG) for ATMPs, working together in collaboration with other stakeholders, have identified a need to develop this guidance to facilitate both NHS sites and industry partners on the use of the current NIHR secondary care tariffs relating to ATIMPs in order to provide transparency and standardisation across UK

There is ongoing work being undertaken with the NIHR Clinical Research Networks and the Advanced Therapy Treatment Centre (ATTC) Industry Advisory Group (IAG) to further develop the iCT but the Pan UK PWG for ATMPs has recognised the need for an interim guidance document to support ongoing activities. This document therefore provides recommendations to support sites in costing clinical trials of ATIMPs, and provides guidance on how to utilise the current NIHR costing tariffs for these studies. As further work is developed, this guidance document will be updated accordingly.

Completing the Pharmacy Industry iCT Clinical Trials of ATIMPs: Considerations and recommendations

A review of the pharmacy sections of the current NIHR tariffs was conducted, taking into account common pharmacy queries on their use. In collaboration with the ATTC and London ATMP networks additional guidance points and clarifications have been provided below, for both NHS sites and sponsors to consider when negotiating pharmacy costs for clinical trials of ATIMPs.

Due to the complexity of ATIMP clinical trials, the majority of the set up activity is undertaken by higher banded staff than for Types A, B or C CTIMP trials. It is important to note that the iCT is set with a standard hourly pharmacy rate based on AfC B7. This base rate is unable to be changed in the iCT but adjustments can be made by NHS sites in terms of time taken to set up the trial to factor in the increased banding (e.g.

increase the time taken to set up if the work is undertaken higher banded staff (B8) is equivalent to 1.2 x base rate to factor only being charged at B7 rate)

1. Considerations when providing a cost for Advanced Therapies): Type D (Cell Based Gene Therapy), E (Virus based Gene Therapy), F (Somatic Cell Therapy) and G (Tissue engineered product)
a) Set Up and Close Down Fees

In the table 1 below common themes for considerations for ATIMPs are highlighted for local sites to take into consideration when costing the time for ATIMP Type D, E, F and G trials.

Current Activities included in the costing template	**Common issues for ATIMP Trials**	**Potential mitigations and considerations**
Feasibility assessment including attending initial feasibility meeting/s	More complex and involve other departments, i.e. Cellular therapy unit, genomics labs, Radiology, external organisations etc. <u>Gene Therapy:</u> Risk assessments are more complex, involving HSE regulations, expert input on risk assessments (GMO safety committee) Review standard SOPs for spillage kits and waste management Pharmacy facility risk assessment of other areas: quality systems (audits) (if reconstitution is happening outside pharmacy) <u>Cell Therapy:</u> Assessing capability, Regulatory gap analysis of: MHRA, GCP, JACIE, HTA IMP Product dossier, Review standard SOPs for spillage kits and waste management Pharmacy facility risk assessment: quality systems (audits) All the above requires greater expertise and more time than less complex trials (type A, B, C)	The NIHR have confirmed that feasibility activity forms part of NHS business service and is captured elsewhere in the NIHR tariff. It is currently included within set up activity and therefore the cost should be adjusted accordingly dependent on time taken for this activity. It is noted that feasibility and/or set up activity undertaken when the study is subsequently dropped by the sponsor is not currently funded and this will be raised as an ongoing query with the NIHR. Activity which is outsourced should be included either within this set-up fee or a separate set up fee charged dependent on how local sub-contracting and/or SLA is implemented. NB. If the activity is acting within a consultant capacity i.e. offering advice on how to deliver the study within the NHS, providing review of sponsor documents prior to finalisation - it is expected a separate contract should exist for this activity. Costs included within the NIHR iCT are to cover real costs to the NHS for the delivery of the trial
Initial communication with the sponsor	More complex and require greater expertise and time than less complex trials (type A, B, C)	This is regarded as set up activity and therefore the cost should be

		adjusted accordingly dependent on time taken for this activity. .
Participation in mandatory local review, completion of risk assessments and approval processes	More complex and require greater expertise and time than less complex trials (type A, B, C)	This is regarded as set up activity and therefore the cost should be adjusted accordingly dependent on anticipated time taken for this activity.
Attendance at meetings & liaison with PI, Research Nurse, CRA	More complex and require greater expertise and time than less complex trials (type A, B, C)	This is regarded as set up activity and therefore the cost should be adjusted accordingly dependent on time taken for this activity.
Write bespoke SOPs, associated documents and worksheets	More complex and require greater expertise and time than less complex trials (type A, B, C)	This is regarded as set up activity and therefore the cost should be adjusted accordingly dependent on anticipated time taken for this activity.
Set up processes with external-to-pharmacy departments or 3rd party providers	Pharmacy oversight: Creation and review of SOPs for external-to-pharmacy departments (spillage kits, oversight when activities happen outside pharmacy) Manipulation of this products may happen in another site within the same trust; risk assessments, creation of SOPs, training, audits, etc.	This is regarded as set up activity and therefore the cost should be adjusted accordingly dependent on time taken for this activity. Ongoing audits of these areas can be justified within the Specialist profession oversight fee
Review of agreements and/or SLAs with any external-to-pharmacy departments or 3rd party providers, if required	Requires high level of expertise to review these documents.	This is regarded as set up activity and therefore the cost should be adjusted accordingly dependent on anticipated time taken for this activity.
Set up dispensing & stock control software systems and documentation	More complex and require greater expertise and time than less complex trials (type A, B, C)	This is regarded as set up activity and therefore the cost should be adjusted accordingly dependent on anticipated time taken for this activity. .
Set-up electronic prescribing and Pharmacy systems, where applicable	More complex and require greater expertise and time than less complex trials (type A, B, C)	This is regarded as set up activity and therefore the cost should be adjusted accordingly dependent on time taken for this activity.. .
Train relevant Pharmacy staff and/or staff at external-to-pharmacy departments or 3rd party providers, as required	Specialist training requirements on handling of ATIMPs for both members of pharmacy staff and staff outside of pharmacy , such as stem cell lab, genomics lab, etc. Out of hours training to on-call staff	This is included as a separate costs: ‘‘Pharmacy Individual training sessions for handling and preparation of study advanced therapy/radiopharmaceutical’ This should be cost should be included within the contract and invoiced at an hourly rate.

Review contract including pharmacy costings	More complex and require greater expertise and time than less complex trials (type A, B, C). May involve negotiating costings for any external-to-pharmacy departments or 3rd party providers.	This is included within set up activity and therefore the cost should be adjusted accordingly dependent on time taken for this activity dependent on anticipated time taken for this activity.
Close down	Final audit of any external-to-pharmacy providers is more time-consuming for pharmacy (e.g. for oversight of ATIMP activities happening outside pharmacy, increase time for cellular therapy)	This could be justified within the negotiated 'Pharmacy Specialist profession oversight fee for advanced therapies or radiopharmaceuticals'

As with all CTIMPs, the below additional activities are not specifically captured in the costing template but should be considered as 'Set up activity' when negotiating ATIMP trials:

- Hourly rate to attend initial meetings during feasibility stages
- Review of waste management local procedures and SOPs
- In depth review of Investigator Brochure and associated documents
- In depth review of PIS
- Time taken to review sponsor/trial regulatory compliance with, for example, the MHRA, JACIE, HTA, GMSC, GMP, GCP.
- Additional SOPs usually required: specific COSHH forms, specialist spillage kits, waste management, product handling, supply, transport between departments, for example when aseptic services units or Stem cell lab are located in different places
- Trial change control
- Validation of new processes and/or equipment
- Consideration to activity when using an external stem cell lab (e.g. NHSBT) and how these costs should be incorporated into the contract.

It is important to note the below points:

- The default fees that are listed in the iCT for Type D, E, F and G trials are a guide. These may be adjusted by NHS sites dependent on the delivery model being used locally.
- To ensure full transparency, it would not be unreasonable to include multiple pharmacy set-up fees where an external-to-pharmacy departments or 3rd party provider is used.
- All changes made to the default costs should be justified with additional noting to provide full transparency to sponsors

b) IMP Management Fee: Considerations for ATIMPs for NHS sites when costing the time for IMP management Fee:

Current Activities included in the costing template	**Common issues for ATIMP Trials**	**Potential mitigations and considerations**
Temperature management activities other than providing evidence of temperature to sponsors	Storage, temperature monitoring and maintenance of equipment is higher due to additional requirements: thawing, transport to other areas or sites within the trust - Add fee for -80^{0}C freezer storage maintenance or provision of freezer if required	This could be justified within the 'Pharmacy Storage space per month to cover charge incurred by Pharmacy for additional space within each NHS Trust regardless of temperature requirements' and 'Pharmacy Specialist storage requirements for advanced therapy/radiopharmaceuticals (e.g. dry shipper containing liquid nitrogen or minus 80C freezers). The charges within the iCT could be adjusted accordingly dependent on anticipated time taken for this activity.
Temperature excursion management	More deviations are expected as more areas to monitor, depending on the complexity of the trial and number of IMP/NIMPs	This could be justified within the IMP Management fee. The charges within the iCT could be adjusted accordingly dependent on anticipated time taken for this activity however, it should be noted that the expectation would be for no excursions.
Transport of ATIMPs	Safe transport from pharmacy/ cell lab to the clinical area.	This could be considered as part of the Advanced Therapy dispensing fee as will occur with every dispensing. The charges within the iCT could be adjusted accordingly dependent on anticipated time taken for this activity.

It is important to note the below points:

- The default fees that are listed in the iCT are a guide. These may be adjusted by NHS sites for all trials types, including Type D, E, F and G trials, dependent on the delivery model being used locally.
- To ensure full transparency, it would not be unreasonable to include multiple IMP management fees where an external-to-pharmacy departments or 3rd party provider is used.
- All changes made to the default costs should be justified with additional noting to provide full transparency to sponsors

c) Specialist profession oversight fee

Current Activities included in the costing template	Common issues for ATIMP Trials	Potential mitigations and considerations
Pharmacy oversight of external-to-pharmacy departments or 3rd party providers	Additional time for review of quality systems including audits and monitoring during the trial (for example if storage or reconstitution is happening outside pharmacy, including thawing of the product)	This could be justified within the negotiated 'Pharmacy Specialist profession oversight fee for advanced therapies or radiopharmaceuticals' based on anticipated time taken for this activity.
Ongoing communications and meetings with sponsor, IMP supplier, and 3rd party providers	More complex and require greater expertise and time than less complex trials (type A, B, C)	This could be justified within the negotiated 'Pharmacy Specialist profession oversight fee for advanced therapies or radiopharmaceuticals' based on anticipated time taken for this activity.
Ongoing training of pharmacy staff and/or staff at external-to-pharmacy departments or 3rd party providers, as required	Specialist training requirements on handling of ATIMPs for pharmacy staff and staff external to pharmacy when activities happen outside pharmacy, such as stem cell lab, nursing staff etc. Out of hours training to on-call staff	This is included as a separate costs: ''Pharmacy Individual training sessions for handling and preparation of study advanced therapy/ radiopharmaceutical' This should be included within the contract and invoiced at an hourly rate.

2. Per Patient Costs

Current Activities included in the costing template	Common issues for ATIMP Trials	Potential mitigations and considerations
Receiving shipment of an autologous ATIMP	Individual shipment for each patient is time consuming.	This is included as a separate cost 'Pharmacy Receiving Shipment'. The default time should be adjusted based on anticipated time taken for this activity.
Collection of autologous ATIMP starting materials	Supply of starting material for autologous products including quality analysis time, testing and facilities cost, such flow cytometry (CD3+, CD19+, CD34+, CD56+) Cryopreservation of starting materials prior to shipping.	It is unlikely this activity would be performed by pharmacy but by an external-to-pharmacy or 3rd party provider. If locally they are considered within the pharmacy costings, consideration should be given to separating these costs for transparency for both the sponsor and external-to-pharmacy or 3rd party provider. NB. This would be charged even if final product was not deemed fit for use.

		The NIHR ATIMP Costing Working Group has engaged with these teams to collate these additional ATIMP Trial costs which are not currently covered within the iCT. Any pharmacy oversight activities associated with collection of autologous materials should be justified within the negotiated 'Pharmacy Specialist profession oversight fee for advanced therapies or radiopharmaceuticals' based on anticipated time taken for this activity.
Ongoing training of pharmacy staff and/or staff at external-to-pharmacy departments or 3rd party providers, as required	Specialist training requirements on handling of ATIMPs for pharmacy staff and staff external to pharmacy when activities happen outside pharmacy, such as stem cell lab, nursing staff etc. Out of hours training to on-call staff	This is included as a separate costs: ''Pharmacy Individual training sessions for handling and preparation of study advanced therapy/ radiopharmaceutical' This should be included within the contract and invoiced at an hourly rate.
Additional dispensing time needed:	For example: - Time for thawing of product - Time for specialist equipment set up including pre and post cleaning times - For gene therapy trials, the use of a dedicated gene therapy isolator time, pre- and post-preparation clean down, may require the draw up from a large number of vials to prepare a single dose	The 'Advanced therapy - additional preparation time' section should be used to reflect these aspects. The default time should be adjusted based on anticipated time taken for this activity.

It is important to note the below points:

- The default fees that are listed in the iCT are a guide. These may be adjusted by NHS sites for all trials types, including Type D, E, F and G trials, dependent on the delivery model being used locally.
- To ensure full transparency, it would not be unreasonable to include 2 separate dispensing fees where an external-to-pharmacy departments or 3rd party provider is used as there is a legal requirement for pharmacy oversight for the dispensing of all ATIMPs.
- Any changes made to the default costs should be justified with additional noting to provide full transparency to sponsors

Discussion and Overall Recommendations

The considerations highlighted in this document have been collated to aid NHS sites and sponsors when costing Clinical Trials of ATIMPs, and can be used to support and provide transparency when negotiating cost with sponsors, providing pharmacy costs for grant applications and when writing local pharmacy costing SOPs.

It is recognised that the pharmacy staff intensity requirements may be considerably higher with ATIMP (Type D, E, F and G) trials and the delivery of ATIMP trials can be complex, potentially involving departments outside of pharmacy. Each study should be assessed based on local delivery and costs amended accordingly based on the information the sponsor has provided.

Sponsor and NHS sites should be aware the default charges listed in the iCT are a guide and these may need to be adjusted locally (either increased or decreased) dependent on the local delivery model being used. Any changes made to the default costs should be justified with additional noting to allow full transparency to sponsors.

The recommendations made in this document will be taken forward to the NIHR Costing Working Group for consideration and for additional narrative to reflect highlighted issues to be included in any future ATIMP costing advice published by the NIHR.

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