DMD HUB

Clinical Trial Costing Guidance for Duchenne Muscular Dystrophy: DMD Hub Toolkit

Version 3, March 2023

SUPPORTED BY

NIHR | National Institute for Health Research

Contents

Section 1 – Description of Document

Document Content

This document has been developed to assist the life sciences industry and study sites with costing commercially sponsored Duchenne Muscular Dystrophy (DMD) clinical trials within the NHS. It is intended to be used as a guidance document to assist with completion of the NIHR interactive Costing Tool (iCT) and should be read alongside the associated NIHR costing guidance and relevant study documents.

Acknowledgements

This guidance has been produced by the DMD Hub Centres of Excellence with input from the DMD Hub sites in the UK.

Usage Disclaimer

The following document is intended for use as guidance only. It is the Sponsor's responsibility to anticipate the correct resource required by each site. It is, however, each local Research and Development (R&D) and Finance team that have the ultimate responsibility for ensuring full cost recovery of any study taking place within their locality, in negotiation with the study Sponsor. This document has not been produced in conjunction with any study Sponsors and is to be used solely as a reference guide to assist with the costing process.

All suggested timings included herein are subject to change and amendment.

Recommendations for additions and amendments should be sent to the DMD Hub Manager, Emma Heslop (Emma.Heslop@ncl.ac.uk).

Section 2 – Scheduled Participant Costs

It is useful to have standard timings for assessments that are commonly included in the budget for clinical trials. This can be agreed within your research team and used as standard unless there are trial-specific changes that need to be made. This is not intended to replace a formal costing review and the protocol and relevant manuals need to be consulted for any adjustments that need to be made on a trial-by trial basis.

The table below provides guidance for costing the most common assessments that are included in DMD trials. The timings are suggested minimums or ranges for the different line items. Natural History Studies (NH), Clinical Trials of Investigational Medicinal Products (CTIMP) and Advanced Therapy Investigational Medicinal Product (ATIMP e.g., gene therapy) trials differ in complexity and therefore the timings may be different, so ensure that you check the protocol carefully when performing your costing review. Ensure that the relevant senior members of your clinical research team perform a final review of the costs before returning them to the Sponsor.

General Activities

Activity Description	Clinical time (minutes)	Nurse time (minutes)	Admin time (minutes)
Informed consent	60 (Natural History) 90 - 120 (CTIMP) 120 - 180 (ATIMP)	30 - 45	
Inclusion-exclusion criteria/patient eligibility assessment	15 - 30	10 - 20	
Medical history/demographics	30 - 60	30 - 60	
Concomitant medication check	20 - 30 (screening)	10 - 15	

Activity Description	Clinical time (minutes)	Nurse time (minutes)	Admin time (minutes)
	15 - 20 (on study)		
Randomisation		15	
Height/weight – ambulant patients	5	10	
Vital signs measurements	5	15	
Physical examination	30	10	
Ricci Clinical Severity Scale	20		
Review of laboratory/blood results	10 - 25		
Blood sample – collection only		30*	
Blood sample – processing		30 – 90**	
Urinalysis – urine collection processing		10	
Clinical review of ECG	15 - 20		
Clinical (cardiologist) review of ECHO	30		
Prescription – production/collection	10	20	
Clinical time per biopsy***	45	30	
Biopsy wound follow up	5 - 10		

Activity Description	Clinical time (minutes)	Nurse time (minutes)	Admin time (minutes)
Review/reporting of participant Adverse Events (AEs)	30	30	15
Case Report Form (CRF) / electronic Case Report Form (eCRF) completion including query resolution (per visit)	30	30	60

* consider the patient population, keeping in mind that it can take a substantial amount of time to collect blood from paediatric patients. Consider adding time to the Unscheduled/Itemised costs to cover additional time taken.

** dependent on the level of processing required – consult the study Protocol for this information.

*** discussion with patient, referral, collection of clinical information for referral. Also nurse time to arrange transfer of sample to the lab, inform ward about admission etc.

Note: for clinical trials involving Investigational Medicinal Product (IMP)s: remember to include drug administration and any post-dose observation time to the Scheduled Participant costs – use the Protocol and Investigator Brochure to determine timings.

Physiotherapy Assessments

Activity Description*	Clinical time (minutes)	Nurse time** (minutes)	Admin time (minutes)
Height – arm span/ulna length (non-ambulant patients)		15	
Weight (non-ambulant patients)		30	
North Star Ambulatory Assessment (NSAA) including time to stand/rise from the floor and time to walk/run 10m		60	

Activity Description*	**Clinical time (minutes)**	**Nurse time** (minutes)**	**Admin time (minutes)**
Timed 4-step test/4 stair climb		20	
100m timed test		20	
Performance of the Upper Limb (PUL)		30 - 45	
9-hole peg test		20	
Six-minute walk test		35	
Time to stand/rise from the floor (if not already included as part of NSAA)		10	
Time to walk/run 10 metres (if not already included as part of NSAA)		10	
Myometry (per muscle assessed)		10	
Range of motion (ankles)		20	
Motor Function Measure (MFM)		75	
ActiMyo – includes set up/phone calls/device checks (note - training will be involved – to cost appropriately)		60 + 60 minutes data collection time	
Egen Klassifikation (EK) Scale		30	
Brooke Scale		10	
Vignos Scale		10	

Activity Description*	**Clinical time (minutes)**	**Nurse time** (minutes)**	**Admin time (minutes)**
Lung Function Tests (FVC, MIP, MEP, SNIP, IC, ERV) (Depends on machine, study and how many assessments are included – check on trial by trial basis)		60 for FVC/machine set up 60 for MIP & MEP in sitting & supine	
Barthel Index		5	
Hand grip strength		20	
Patient Reported Outcome Measures		30 per PROM	
Reachable Workspace		90	
Hand Held Dynamometry		45	
NSAD		60	
Muscle testing (Myoquad)		30	
Muscle testing (Myalgia assessment)		15	
The Quick Motor Function Test (QMFT)		5	
Beiring Sorenson test for prone back extensor strength		10	
Filming of assessments: preparation and upload (per filmed assessment)		60	

* this covers the time taken for the full procedure, including setting up, preparing, and delivering the assessment

** physiotherapist time is costed in the ‘Nurse time’ column. It is important to ensure that this is reflected correctly i.e., ensure that the salary band for the Nurse Staff matches that of the Physiotherapists that are working on the study. If not, the time needs to be adjusted appropriately.

Section 3 – Costs to Consider

Ongoing confirmation of consent

It is good practice to confirm participants' ongoing consent to participate in a study at the beginning of every visit. Consider adding 5 minutes per visit in the Scheduled Participant costs for a delegated member of staff to re-confirm/record ongoing consent.

Formal re-consent

Consider including time in the Unscheduled/Itemised costs for the Principal Investigator (PI) or delegated member of staff to re-consent any participants, as necessary (e.g., if there is a protocol amendment which includes changes to the Patient Information Sheets and Informed Consent Forms). Time taken to re-consent a participant will be similar whether this is done face to face or remotely – approximately 30 - 60 minutes medical time and 15 - 30 minutes nurse time on average (this can vary depending on the amendments that have been made – safety amendments can require more time for discussion).

Monitoring visits

Monitoring visits entail clinical, nurse and admin time and can involve a lot of work, particularly for the Data Manager. The monitor will usually want to spend some time with the PI or Sub-Investigator (30-60 minutes) and the Data Manager/Nurse/possibly Physiotherapist will need to be available during the visit to answer queries. Remote monitoring calls should be charged at an hourly rate for the staff involved. These visits/calls can be costed in the Scheduled Participant costs or the Unscheduled/Itemised costs: speak to your research team to decide which is most appropriate.

Coordination/support for participant appointments

Organising participant appointments (arranging a suitable date, organising travel and accommodation, arranging the visit around staff availability and the need to rearrange this if necessary) can take a lot of time and should be costed within the Scheduled Participant costs. Discuss with the member of staff that will be responsible for arranging participant appointments/travel/accommodation etc. to agree an appropriate time per visit for visit coordination (this will depend on the demands of the study i.e., if accommodation needs to be booked, if coordination is required between several support departments), but a minimum of 30 minutes per visit for the appropriate member of staff is advised.

Admin time for the PI, Nurse, and Physiotherapist

Time is spent by the PI, Nurse and Physiotherapist before/during/after each visit preparing study documents and equipment, writing up assessment results, signing forms etc. This time can add up and should therefore be costed. Adding 30 minutes of admin time per visit for the PI, Nurse and Physiotherapist in the Scheduled Participant costs can help to cover these additional duties.

Additional admin time

Consider adding 60 minutes Clinical, Nurse, Physio and Admin time to the Unscheduled/Itemised costs to account for training, amendment training, teleconference time with Sponsor or to account for additional work created as a result of unforeseen events on the study – charged at an hourly rate. Clinical Trial Coordinators are often also required to perform training so discuss with your local team how best to cost this time at the appropriate salary level (given that there is no 'Trial Coordinator' option on the costing tool).

Consultation with a specialist if required in the event of an AE

Consider adding 30 minutes medical time to the Unscheduled/Itemised costs to cover time spent by the doctor/PI consulting with a specialist medical professional in the event of an AE/SAE.

Review/reporting of SAEs

Consider including 60 minutes medical time, 30 - 45 minutes nurse time and 20 - 30 minutes admin time in the Unscheduled/Itemised costs to cover additional review and reporting time for SAEs.

Physiotherapist reliability training

For trials that include physiotherapy assessments, consider adding 60 minutes to the Unscheduled/Itemised costs to cover reliability training (to be charged at an hourly rate) – if relevant.

Overnight stays

If participants are required to stay overnight (for multiple day visits, or visits starting early in the morning/lasting until late at night

when participants live a distance from the research site etc.), ensure that these are costed appropriately in the Scheduled Participant costs for the relevant visits. Consider also adding an overnight stay to the Unscheduled/Itemised costs in case of an additional stay being needed. Consider whether the overnight stay can be in a local hotel (a preferential rate may be able to be negotiated if this is going to be a regular hotel used for booking overnight stays for study participants). If the participant stay needs to be as an inpatient/within the Clinical Research Facility, this also needs to be costed appropriately by consulting with your local team. Things to consider: facility/room hire fees, meal costs, lab processing if needed. Medical supervision within the hospital should be costed at an appropriate rate and if the PI has to be available in case of any issues, consider costing this clinical time in Unscheduled/Itemised costs to be charged for as applicable.

Unscheduled visits

On occasion, unscheduled visits need to take place e.g., to repeat an assessment or take an additional blood sample. This should be addressed in the Unscheduled/Itemised costs/Clinical Trial Agreement with a statement to request that assessments that are conducted as part of an Unscheduled Visit will be costed as they appear in the Scheduled Participant costs. Unscheduled visits can vary in complexity and coordinating these visits can be time consuming, so remember to charge for this additional time if appropriate (e.g., under the additional admin time item, as above).

Additional assessments

In the protocol, it may state that additional assessments may be performed, at the discretion of the Investigator and Medical Monitor e.g., blood results may need to be repeated. Consider adding these assessments to the Unscheduled/Itemised costs. If the assessment is a sample that needs to be processed/sent away, include these costs also.

Lab tests that may need to be performed (urgently) at another lab

Some tests may not be offered at your local lab so if they must be performed locally as per protocol, you may need to arrange to have the samples sent to another local lab for processing. Discuss this with your study team/Sponsor and if appropriate, ensure that the required arrangements are put in place in advance (e.g. a Service Level Agreement with the external lab, agreement on how this will work logistically) and that the relevant costs (including transport of the sample to the lab as well as the cost of the actual test itself) are included in the Scheduled Participant costs or Unscheduled/Itemised Costs, whichever is most appropriate.

Coordination of participants to other departments

If the study involves the participant attending a number of departments within the hospital as part of their visit and a member of staff is required to accompany them, discuss this with the relevant member of staff and input time into the Scheduled Participant costs accordingly to cover this.

Autopsy

If there is an autopsy or autopsy report mentioned in the trial protocol/schedule of events, check the specific wording and whether there is consent for autopsy included in the patient documents. Cost this as appropriate, in the Unscheduled/Itemised costs. Ensure that this is discussed with the PI and relevant teams during setup. If an autopsy is requested (rather than a copy of a report), this can create logistical issues that need to be addressed and costed e.g. arranging transport of a body from another location to the study site (and back again in an appropriate timeframe) and the logistical considerations that this will entail, whether there is capacity for a clinical research autopsy to be conducted on-demand, consideration of the procedures that need to be performed/samples taken and how these will be stored and shipped etc.

Support department costs

Include setup costs for the departments that are involved in the study, as appropriate (in the Setup & Closedown Costs). Without the support of different departments within our hospitals, we would not be able to carry out our research, so it is important that the relevant departments are paid for the work that they do. Discuss this with the support departments and your R&D/Finance teams to ensure that costs are being allocated appropriately.

Setup and closedown costs

Ensure that what is included in the costing tool and contract reflects what your team/Trust would expect in terms of payment for amendments and any stipulations around screen failures (will your team/Trust accept a cap on the number of screen failures that will be paid for?). Ensure that a closedown fee is also included, to cover relevant study closedown activities.

Upfront costs

At times, it may be appropriate to request an upfront payment from the study Sponsor in order to employ a member of staff to work on a study. This would need to be appropriately justified to reflect the percentage of a Whole Time Equivalent (%WTE) member of staff required i.e., total staff time for relevant study assessments x number of recruits = total hours (which can be converted into a %WTE member of staff). Once a %WTE is determined, you should then obtain a quote from your Finance department for the relevant staff salary so that the PI can put the full request to Sponsor. If agreed, the associated timings for that member of staff should be removed from the Scheduled Participant costs and a lump sum cost for the staff salary be entered into the costing tool (speak to your R&D/Finance team to agree the best place to put this within the study budget). The payment schedule for these upfront costs should be properly set out in the Clinical Trial Agreement. It should be made clear that payment of the salary is not linked to achievement of a local recruitment target or to the efficacy of the study and will be paid upfront at the beginning of the study, at the Sponsor's own risk.

General consideration

It is very easy for items to be missed when they are costed under the Unscheduled/Itemised activities, as they are not routinely invoiced for in the same way as the Scheduled Participant activities. Therefore, it can be useful to include as many elements as possible in the Scheduled Participant costs (as long as this is appropriate), to make invoicing easier.

Home nursing

When a trial involves a home nursing vendor for dosing or specific trial assessments, ensure that appropriate time is also costed in for the Nurse and PI for the activities that they may carry out surrounding the home nursing visits. E.g., consider adding 45-60 minutes Nurse time per visit to the Scheduled Participant costs to account for liaising with the home nursing vendor to organise/feedback on the home visits and liaising with the vendor to organise IMP delivery. Also consider adding 60 minutes medical time to the Unscheduled/Itemised costs for the PI to review any changes to medication reported/adverse events – to be billed for, as necessary.

Flexibility to adapt to changing circumstances

The Covid-19 pandemic has taught us a lot about how clinical trials must be flexible to adapt to different circumstances. It is important to remember that sites must be paid for the work that they carry out to deliver studies, whether this is remotely, face-to-

face, or a mixture of both. Consider whether, when circumstances change, re-costing is strictly necessary as this can take a lot of time and effort. The DMD Hub can help with these discussions with study Sponsors.

Set up & Closedown Costs – set up and Chief Investigator fees

Discuss within your research team the appropriate set up fees for clinical trials - this may differ for ATIMPs, Phase 1/2 CTIMPs, Phase 3/4 CTIMPs and Natural History or Long term follow up trials due to the differing complexity of the set-up processes involved. Having these agreed in advance with appropriate justifications is useful, as is having agreed Chief Investigator fees for the different categories of trials.

Costing a study properly is important as it helps to ensure that appropriate time is allocated to carry out the tasks involved.

Section 4 - Costing Guidance for DMD Gene Therapy Clinical Trials

Costing gene therapy clinical trials is a complex process, due to various factors such as the nature of the ATIMP and also the characteristics of gene therapy protocols that are designed to closely monitor participant safety.

The guidance below is not an exhaustive list, and will evolve with time, but provides a useful reference point when costing gene therapy trials.

Ensure that you perform the usual costing review with the study PI and other relevant members of staff to make sure that they are happy with the line-item timings in the costing tool. This guidance is not intended to replace a formal costing review.

Set-up fee

As setting up gene therapy trials is complex and requires significant input from the Clinical Trial Coordinator as well as other members of staff, consider whether an increased set up fee is appropriate. The additional complexity of set up includes facilitating Genetic Modification Safety Committee (or equivalent) Risk Assessment and review, oversight of additional safety requirements for delivery teams/support departments, additional complexities surrounding organising participant accommodation/travel and potential additional cleaning and waste management requirements (to list only a few).

Safety Task Force

The Safety Task Force is a model that has been developed in Newcastle for the safety oversight of gene therapy patients. It is a multidisciplinary group of specialists that can work together to support the safe delivery of gene therapy trials within a specific location, and this can also be extended to the administration of licensed gene therapy products within that location. The main role of the group is to advise on and coordinate patient management in case of post-treatment complications and to act as first point of contact in the relevant specialties for if and when they are needed (e.g., to manage AEs).

Due to the coordination required in establishing and communicating with the Safety Task Force, this must be adequately resourced. The time spent by the specialists who make up the Safety Task Force must also be appropriately acknowledged.

If a Safety Task Force model is adopted at your site, we would recommend communicating with your R&D Department and Governance team to discuss how this activity can be appropriately managed and resourced within your Trust. The DMD Hub team can put you in touch with the relevant members of staff in Newcastle if you would like further information about the Safety Task Force.

Additional points to consider: immune response considerations (check with PI)

Discuss with your local PI whether the provision of Eculizumab (Soliris) should be included in the Unscheduled/Itemised Activities for the study. Eculizumab is used to mediate an immune reaction that may occur as a result of receiving the gene therapy/viral vector.

If this is required, include this in the costing with a 'zero' cost. Detail 'as per BNF, plus VAT' in the notes and ensure that this is copied over into the contract. BNF is the British National Formulary and listing the cost 'as per BNF, plus VAT' ensures that, should the drug be required (as it is expensive), it will be charged as per the cost at the time of ordering.

- Ensure that Eculizumab is available on site prior to dosing. Eculizumab may therefore need to be costed in Set Up costs or an agreement reached with Sponsor that it will be provided to site prior to dosing/shipped with the drug.
- Sites will need to have the meningococcal vaccine available in case of administration of eculizumab – discuss the appropriate costing for this with the Pharmacy team.

In the protocol for gene therapy trials, participants are generally prescribed high-dose steroids around the administration of gene therapy, to help to mediate the immune response associated with the viral vector, and these are gradually tapered following the gene therapy administration. Following this tapering, if the participant fails to produce the required level of the hormone cortisol themselves, they may go into multiple organ failure. In order to test for this, a Cortisol serum test (ACTH Stimulation/Synacthen Test) may need to be costed into the trial as part of the battery of laboratory tests. You should discuss whether this is needed and when it should be carried out with the PI during set up – they will need to discuss this with the Sponsor if this is not already included in the protocol.

Scheduled/All Participants

- Informed consent takes significantly longer for ATIMP trials (guide – 120 – 180 minutes medical time)

- Ensure that accommodation and cleaning requirements are appropriately costed, depending on the length of time that the participant must be accommodated, where (hospital or nearby hotel/apartment) and any isolation and cleaning requirements

- Related to the above, ensure that any specific local requirements as per GMSC or Safety Task Force recommendations are costed for e.g., PPE

- Consider including additional PI time for an end of trial handover to the patient's local Standard of Care team

Unscheduled/Itemised Activities

- Discuss with the PI during set up whether there are any additional lab tests that they may wish to repeat or perform locally and include these in the Unscheduled/Itemised Activities

- There is often a lot of training requirements for gene therapy trials – ensure that time is costed into the Unscheduled/Itemised Activities to cover this for all members of staff, for training during set up (pre-activation) and updates throughout the trial as well as amendments

- Related to the enhanced safety monitoring for gene therapy trials, cost in time for the PI to consult with a specialist (e.g., respiratory consultant, cardiologist, nephrologist) if required in the event of an AE – Medical time, per hour

- If the participant is not local, the PI will need to communicate with their local consultant/team to explain the trial and provide patient updates (e.g., quarterly)

Please also refer to the following guidance:

- Clinical-trials-toolbox.pdf (kxcdn.com) (ATIMP Costing Guidance section)

- https://www.sps.nhs.uk/wp-content/uploads/2022/07/Costing-Clinical-Trials-of-ATIMPs-using-the-interactive-Costing-Tool.pdf- this guidance is relevant to Pharmacy but also gives a good overview of the additional activities that are performed and that can justify an increased set up fee for ATIMP trials