Evaluation of the Gene Therapy Patient Referral Pathways in the UK

White Paper

2023

Cell and Gene Therapy Catapult, DMD Hub, Newcastle University, Northern Alliance Advanced Therapies Treatment Centre

Project delivery team

Cell and Gene Therapy Catapult: Daniel Baston, Quality and Standards Manager

DMD Hub and Newcastle University: Emma Heslop, DMD Hub Manager; Megan McNiff, Research Associate; Phillip Cammish, Central Recruitment Database Manager; Anna Irvin, Senior Clinical Trial Coordinator

Northern Alliance - Advanced Therapies Treatment Centre: Catherine Van Niekerk, Lead Project Manager

Acknowledgements

The DMD Hub (www.dmdhub.org) is a collaboration between The John Walton Muscular Dystrophy Research Centre at Newcastle University and the Newcastle upon Tyne Hospitals NHS Foundation Trust, and Duchenne UK.

Pfizer Ltd provided financial support, but had no influence in the initiation, development or delivery of this project.

Special thanks to the clinical teams who took part in this study including:

- Dr Chiara Marini-Bettolo, Consultant Neurologist, Honorary Senior Clinical Lecturer, Clinical Lead and Professor Michela Guglieri, Professor of Neuromuscular Disorders, Honorary Consultant Neurologist, Clinical Research Strand Lead; The John Walton Muscular Dystrophy Research Centre, Translational and Clinical Research Institute, Newcastle University and Newcastle Hospitals NHS Foundation Trust
- Dr Anne-Marie Childs, Consultant Paediatric Neurologist, Leeds Teaching Hospitals NHS
- Dr Imelda Hughes, Consultant Paediatric Neurologist and Dr Gary McCullagh, Consultant Paediatric Neurologist, Manchester University NHS Foundation Trust
- Dr Anirban Majumdar, Consultant paediatric neurologist, Natalie Fineman, Lead Research Nurse and Tracey Bingham, Senior Research Nurse; Bristol Royal Children's Hospital at University Hospital
- Dr Min Ong, Paediatric Neurology Consultant (Neuromuscular), Sheffield Children's NHS Foundation Trust
- Dr Mariacristina Scoto, Neuromuscular Consultant, Great Ormond Street Hospital

Publication date

August 2023

Point of Contact

DMD Hub: dmdhub@newcastle.ac.uk

Executive Summary

This is a collaborative project between the Cell and Gene Therapy Catapult (CGT Catapult), the DMD Hub (Newcastle University) and the Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC), that aims to identify and analyse the gene therapy patient referral pathways in the United Kingdom.

The advancement of gene therapy clinical trials in Duchenne muscular dystrophy (DMD), and the recent accelerated approval of a gene therapy product for use in a limited cohort of DMD patients in the United States, indicates an immediate need to discuss gene therapy and the referral processes for DMD patients in the UK.

Neuromuscular consultants with experience in either referring or accepting patients for gene therapy clinical trials or licenced gene therapy products, completed an online survey and follow up interview to understand their experiences with gene therapies. These answers allowed critical analysis of the referral processes for clinical trials and licenced gene therapy products and define the requirements for high quality referrals for gene therapy in DMD.

By highlighting best practice from across the UK, we propose a referral pathway for gene therapy clinical trials in the UK, to allow effective and equitable access to research for DMD patients. As gene therapy is on the horizon for DMD as a licenced product, we considered how we can prepare for gene therapy licenced products in DMD as standards of care, using learnings and shared experiences from approved gene therapies in other neuromuscular disorders. A set of recommendations for improved, standardised future practice is proposed, as well as referral pathways for gene therapy clinical trials and licenced products for DMD.

Table of Contents

Abbreviations

AAV	Adeno-associated virus
CPD	Continued professional development
CRD	DMD Hub Central Recruitment Database
DMD	Duchenne muscular dystrophy
EAMS	Early access to medical scheme
FDA	Food and drug administration
MDT	Multi-disciplinary team
NICE	The National Institute for Health and Care Excellence
NA-ATTC	Northern Alliance Advanced Therapies Treatment Centre
NHSE	National Health Service England
SMA	Spinal muscular atrophy

Introduction

Duchenne muscular dystrophy (DMD) is a progressive muscle wasting condition resulting in a reduced life expectancy (median 28.1 years) (1). The disease is caused by mutations in *DMD* gene located on the X chromosome, which encodes the protein dystrophin (2). As DMD is an X-linked condition, the vast majority of those affected are males, with a prevalence of 20 per 100,000 live male births (3). Female carriers are often asymptomatic, although some show heart involvement and weakness and wasting of skeletal muscle with varying severity (4,5).

The lack of functional dystrophin in muscle leads to progressive muscle damage, increased fibrosis, and replacement of skeletal muscle with fat. Symptoms typically present in the first years of life, with the average age of diagnosis for DMD in the UK being 4.3 years (6). Patients typically lose independent ambulation and require a wheelchair by the age of 12, followed by scoliosis, loss of upper limb function, respiratory insufficiency and cardiomyopathy (7).

Introduction of multidisciplinary care, improvements to the standards of care for DMD (8–10), including the use of corticosteroids (11,12), has increased the survival of DMD patients. Standards of care are currently focused on the management of symptoms, highlighting an unmet need for treatments targeting the cause of the disease. Currently, clinical trials in DMD are focused on both reducing the secondary consequences of dystrophin deficiency and restoring dystrophin production (13).

Gene transfer therapy (termed gene therapy hereafter) involves the delivery of a functioning copy of the dystrophin gene in order to produce a partially functional protein to the targeted muscle cells (14). The delivery is by a viral vector, specifically an adeno-associated virus (AAV) (15). The *DMD* gene is the largest in the human genome, and so a truncated version is used in gene therapy medicinal products, delivering 'micro-dystrophin' to the patient's muscle. This means that, even if effective, gene therapy in DMD will not be a cure, but in theory could lead to the production of a truncated dystrophin protein, similar to the one described in patients with the milder Becker muscular dystrophy phenotype (16). Patients can be exposed to AAV throughout their daily lives, which can generate immunity to the therapy, so they must be screened by an AAV antibody test prior to receiving the treatment.

There are currently four gene therapy medicinal products being investigated in clinical trials in DMD (17,18), with two of these products being tested in phase three clinical trials in the United Kingdom (UK) at the time of writing (19,20). There are significant risks in participating in a gene therapy clinical trial; there have been serious adverse events, clinical holds and two deaths reported involving the use of AAVs (21,22). However, there is promise for the future of gene therapy, with Sarepta's gene therapy product ELEVIDYS being granted accelerated approval by the Food and Drug Administration (FDA) in the United States in June 2023 for four to five year old boys with DMD (23).

Currently, the processes for patients receiving gene therapy medicinal products across the disease spectrum in trials and as part of standard care are variable. Clinicians often rely upon locally held registries and require specialist knowledge about available treatment options. As the spread and scale of gene therapy clinical trials widens, efficient and effective processes for referring patients will be required to avoid any impact on treatment efficacy, ensure patient access to trials, and maximise opportunities for clinical sites to recruit. In addition, understanding and reviewing the existing clinical referral pathways for clinical trials and clinical care and considering what works well and

what could be improved will allow us to be well prepared when it comes to ensuring equitable access to approved gene therapy products in DMD.

This collaborative project between the Cell and Gene Therapy Catapult (CGT Catapult), the DMD Hub (Newcastle University) and the Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC) aims to identify and analyse the patient referral pathways for gene therapy in DMD in the UK. Drawing from best practice, a referral pathway for gene therapy clinical trials in the UK has been proposed, to allow effective and equitable access to research for DMD patients. As gene therapy is on the horizon for DMD as a licenced product, consideration has been given to how the UK can prepare for gene therapy licenced products in DMD as standards of care, using learnings and shared experiences from the recent approval of onasemnogene abeparvovec-xioi (Zolgensma), a gene therapy medicinal product approved to treat spinal muscular atrophy (SMA) in the UK (24).

The DMD Hub (www.dmdhub.org) is a collaboration between the UK neuromuscular centre of excellence in Newcastle (The John Walton Muscular Dystrophy Research Centre at Newcastle University and the Newcastle upon Tyne Hospitals NHS Foundation Trust) and the leading UK medical research charity for DMD, Duchenne UK. The DMD Hub is ideally placed to support implementation and improvements in patient referrals for clinical trial and licensed gene therapies. It has already undertaken work surveying the institutional readiness of existing and potential gene therapy clinical trial delivery sites and engaged patients and healthcare professionals on the current barriers to inclusive participation and recruitment in clinical trials. Building on this engagement work, the DMD Hub has developed a centrally coordinated national recruitment database of people living with DMD that are interested in participating in clinical research studies (www.dmdhubrecruits.org). This work will be leveraged in this project to ensure there is no duplication of effort.

Methods

Cell and Gene Therapy Catapult (CGT Catapult) identified and coordinated the delivery team, including the Duchenne muscular dystrophy (DMD) Hub, (Newcastle University and the Newcastle upon Tyne Hospitals NHS Foundation Trust) and the Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC). This study aimed to identify and analyse the gene therapy medicinal product clinical trial patient referral pathways in the UK, with a focus on DMD.

Pfizer Ltd provided financial support for this project in the form of a grant to CGT Catapult Ltd. Pfizer Ltd have had no influence in the initiation, development, or delivery of this project, nor have they influenced the development or content of any materials produced as an output of this project.

Objectives of the project include:

- Work with healthcare professionals to define requirements for high quality referrals for gene therapy in DMD.
- Critically analyse referral processes, highlighting best practice and evaluating root causes for ineffective approaches.
- Produce set of recommendations for improved, standardised future practice, and propose referral pathways for clinical trials and licenced products.

A survey was developed to meet these objectives. Themes of the survey were developed through discussions with key opinion leaders and project staff representing the DMD Hub (Newcastle University and the Newcastle upon Tyne Hospitals NHS Foundation Trust), CGT Catapult and NA-AATC.

The survey was designed and made available online via Jisc Online Surveys and responses were collected between 9th February and 18th April 2023. Qualitative responses were collected by single option questions (yes, no, other) and free text boxes. No incentives were offered for completion of the survey. The consent agreement for taking part in the survey can be found in Appendix 1.

The DMD Hub contacted selected neuromuscular consultants who were part of the DMD Hub Clinical Network and North Star Network to take part. The North Star (www.northstardmd.com) is a well-established clinical network of sites who provide care to patients with DMD. While sites across England and Scotland were contacted, responses were received from sites within England only. There are not currently DMD clinical trial sites in Wales or Northern Ireland. Recommendations throughout this document are applicable to devolved equivalents across the UK. Selected sites had experience in at least 2 of the following:

- Referring patients for gene therapy clinical trials for DMD.
- Accepting referred patients for gene therapy clinical trials.
- Referring patients for SMA gene therapy licenced products.
- Being one of the four commissioned sites for delivery of SMA gene therapy Zolgensma.

Upon completion of the survey, a one-hour interview was carried out with the clinician by DMD Hub team members to clarify and expand upon points made within the survey.

Responses from the survey and the interview transcripts were collated in Microsoft Excel and analysed by the delivery team. Key messages from each section of the survey were summarised and

used to develop a proposed patient referral pathway for clinical trials and for a prospective licenced product.

Results

Neuromuscular consultants from six NHS sites across England took part in the survey and interviews. All had experience in accepting patients referred from other sites and referring patients for clinical trials in DMD. Additionally, three of the sites had experience in accepting patients for the approved gene therapy treatment in SMA, with the remaining three having experience in referring patients for gene therapy in SMA. The results in this document summarise both the survey results and the interview responses from all participants.

Clinical trials patient referral pathways

With at least four companies opening DMD gene therapy clinical trial in the UK and more than seven trials in the clinical development pipeline, it is important to discuss and agree how patients who are interested in taking part in the trials can be assured there is a fair referral process in place. There should be a streamlined and coordinated process for clinicians to refer patients to a trial, particularly as the number of places available and number of sites are limited.

Sites running the trials also need to be reassured that there are processes to facilitate identification of potentially eligible patients, ensuring that recruitment to time and target is possible, particularly given the strict inclusion criteria of most trials.

Workforce planning

Access to clinical research and clinical trials should be seen as an integral part of patient care within the NHS. An effective patient referral pathway to clinical trials is therefore critical to ensure equitable access to clinical research across the country, regardless of where the patient lives or is seen for standards of care clinical follow ups.

Sites are not confident in the support for infrastructure needed to deliver gene therapy trials at present. The majority of respondents to the survey believe that their site/NHS Trust has not invested enough in the infrastructure needed to effectively refer patients to gene therapy clinical trials at other sites.

The focus for investment is at sites delivering treatment. However, a proportion of mandatory care for gene therapy medicinal products is the responsibility of the referring site, e.g. pre assessment screening and post treatment monitoring, which is not financially compensated for. If sites do not have adequate capacity for clinical trials, then their focus will be on delivering clinical service. Furthermore, if a site is chosen to be a commissioned site for gene therapy medicinal products as a part of their clinical service, they may no longer have the capacity for clinical trials as they are often reliant on the same workforce.

Ensuring there is the appropriate workforce of skilled staff to deliver gene therapy clinical trials comes down to capacity, retention and recruitment. While sites have skilled staff, if the capacity is not sufficient they will be unable to take on trials. Improving the retention and satisfaction of skilled staff and streamlining the lengthy NHS recruitment process will ultimately help increase capacity at

sites and allow more clinical trial opportunities and more patients to be recruited to clinical trials across the UK.

The DMD Hub is improving access to clinical research opportunities by developing new and enhancing existing infrastructure for DMD clinical trials within the UK. Since 2017, 34 staff at 11 clinical trial sites have been funded by Duchenne UK as part of the DMD Hub, which has successfully expanded the capacity for sites to run clinical trials, including gene therapy trials, and facilitated an increased number of opportunities for patients to participate in research.

The Central Recruitment Database, (CRD) is an initiative set up in 2022 by the DMD Hub and funded by Duchenne UK, in response to the need from the patient and clinical community, to provide a national contact list of patients with DMD interested in participating in research studies. The CRD facilitates fair and equitable access to clinical trials in the UK by centrally coordinating referrals of potentially eligible patients to recruiting trial sites. The DMD Hub CRD is a collaborative project between the patient organisation Duchenne UK and Newcastle University. The NHS has not been directly involved in the set up or sustainability of this.

Ensuring there is the appropriate workforce of skilled staff to deliver gene therapy clinical trials comes down to capacity, retention and recruitment. While sites have skilled staff, if the capacity is not sufficient they will be unable to take on trials. Improving the retention and satisfaction of skilled staff and streamlining the lengthy NHS recruitment process will ultimately help increase capacity at sites and allow more clinical trial opportunities and more patients to be recruited to clinical trials across the UK.

Recommendation:

NHS England (NHSE), and devolved equivalents, should play a key role in ensuring that adequate and sustainable infrastructures are in place for effective patient referrals to gene therapy clinical trials.

Education, training and CPD

It is difficult to forecast staff training without knowing the sites' role in upcoming potential clinical trials. Clinical service delivery will trump research needs if capacity needs are not met within a trust or board, leading to different educational needs.

It was highlighted that while educational resources and continued professional development (CPD) are available, they are poorly signposted, and sites have to actively research where they can receive training on gene therapy medicinal products in DMD. Sites specifically mentioned Innovate Manchester Advanced Therapy Centre Hub (iMATCH), which is a part of the Advanced Therapy Treatment Centre (ATTC) network, which provides resources and webinars (25). The DMD Hub also provides a selection of online resources and webinars through the DMD Hub Toolkit as well as educational workshops for nurses and clinical trial coordinators.

However, education and training are critical in ensuring safe and effective clinical trials. Allowing training certifications or competencies to be transferable between sites (and within sites between

clinical service and research) would allow staff to be flexible and move between departments and trusts/boards if required. Currently training is provided by individual companies on specific clinical trials. However, access to these training opportunities is only available once a site has been selected for the clinical trial and does not allow the development of expertise to increase trial capacity for gene therapy trials. Neuromuscular disorders, clinical research and gene therapy medicinal products are not currently included in the portfolio/training programme for doctors, therefore it is difficult to attract doctors to specialise in these areas.

Recommendation:

Providing specific gene therapy training and education opportunities, and supporting accessibility, doctors and other healthcare professionals could be better attracted to the specialty of neuromuscular disorders. This would benefit DMD as well as other disease areas where gene therapy is in development as a potential therapeutic approach.

Number of sites running clinical trials

Four sites including Alder Hey Children's Hospital, Great Ormond Street Hospital, the Newcastle upon Tyne Hospitals NHS Foundation Trust, and Oxford University Hospital are currently running clinical trials for DMD gene therapy medicinal products in the UK. Additional capacity will be needed to meet the growing demands of upcoming gene therapy medicinal product clinical trials in DMD.

Clinicians surveyed agreed that the limited number of UK sites currently selected by industry to run gene therapy clinical trials is not sufficient to meet future demands. Increasing the number of sites with the skills and experience to deliver gene therapy would help ensure there is the capacity to run the upcoming (and future) clinical trials, as well as having a direct impact on the ability to deliver and monitor licenced gene therapy medicinal products (as more sites will have experience) if and when approved. It would also reduce the burden for families having to travel long distances to take part in trials, or allow families who may not have the resources to support the costs of travel, missing work and providing care to family remaining at home, to take part where this previously was not possible.

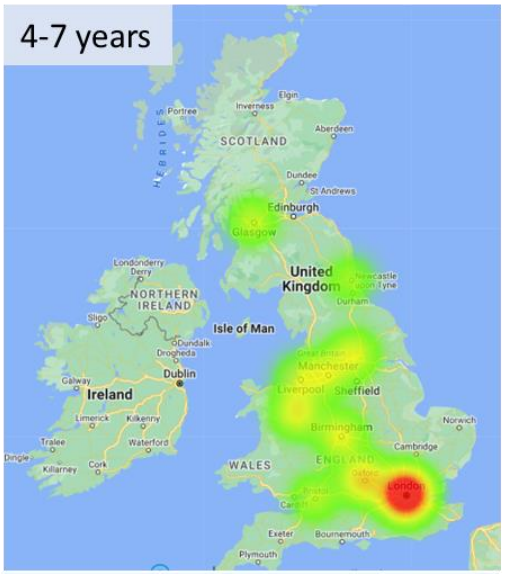
In addition to skills, expertise and capacity of sites, geographical spread should be taken into consideration when deciding where to locate further sites for clinical trials. On average, sites estimated an additional two sites (six in total) to meet demand and allow for effective recruitment, which is often delayed by capacity issues and safety monitoring at a site.

The DMD Hub recently completed a capacity survey from DMD clinical trial sites across the UK. Figure 1 shows a heat map of the geographical spread of patients in different age ranges registered at specialist neuromuscular clinics. There are currently no DMD Hub sites in Wales or Ireland, and this will need to be addressed to improve fair and equitable access to clinical trials.

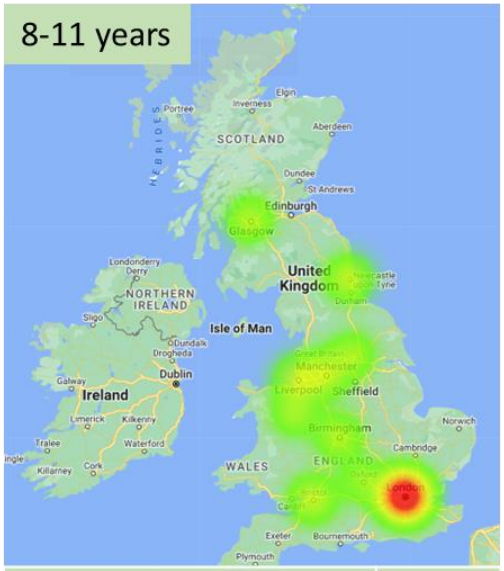
Recommendation:

Consider where additional clinical trials sites for future gene therapy trials should be located geographically to ensure equitable access to clinical trials. Explore resources and facilities in areas currently not covered for the delivery of clinical trials (e.g. Wales, Northern Ireland) and invest in developing infrastructures to deliver clinical trials (and approved medical products) in the future.

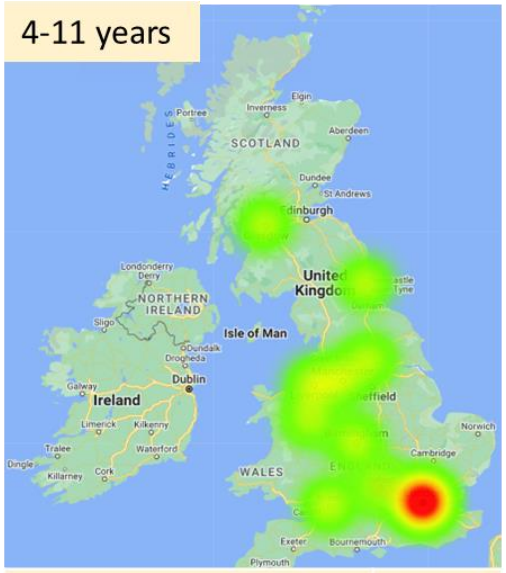
Figure 1: Geographical distribution of patients by age. *Heat map showing distribution of patients located at DMD Hub sites across the UK by age ranges.*



DMD Hub Site	Population
Alder Hey Children's NHS Foundation Trust	10
Bristol Royal Hospital for Children	9
Birmingham Heartlands Hospital	14
Evelina London Children's Hospital	23
Great Ormond Street Hospital NHS Foundation Trust	35
Leeds Teaching Hospitals NHS Trust	13
MDUK Oxford Neuromuscular Centre, University of Oxford	20
Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust	7
Robert Jones and Agnes Hunt Hospital	15
Royal Hospital for Children, Glasgow	10
Royal Manchester Children's Hospital	11
Total	**167**



DMD Hub Site	Population
Alder Hey Children's NHS Foundation Trust	20
Bristol Royal Hospital for Children	21
Birmingham Heartlands Hospital	17
Evelina London Children's Hospital	27
Great Ormond Street Hospital NHS Foundation Trust	71
Leeds Teaching Hospitals NHS Trust	15
MDUK Oxford Neuromuscular Centre, University of Oxford	13
Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust	20
Robert Jones and Agnes Hunt Hospital	15
Royal Hospital for Children, Glasgow	18
Royal Manchester Children's Hospital	18
Total	**255**



DMD Hub Site	Population
Alder Hey Children's NHS Foundation Trust	30
Bristol Royal Hospital for Children	30
Birmingham Heartlands Hospital	31
Evelina London Children's Hospital	50
Great Ormond Street Hospital NHS Foundation Trust	106
Leeds Teaching Hospitals NHS Trust	28
MDUK Oxford Neuromuscular Centre, University of Oxford	33
Newcastle University and The Newcastle upon Tyne Hospitals NHS Foundation Trust	27
Robert Jones and Agnes Hunt Hospital	30
Royal Hospital for Children, Glasgow	28
Royal Manchester Children's Hospital	29
Total	**422**

Network between referral centre and clinical sites – hub and spoke model

The DMD Hub and specifically the DMD Hub CRD were highlighted as established infrastructures already utilised by sites to accept or refer patients for clinical trials, which are funded by Duchenne UK. The North Star network was previously utilised by clinicians in a less structured way, as a means of identifying potentially eligible out-of-area patients for recruitment to clinical trials, when recruitment target could not be reached within the patient list at the trial site.

The DMD Hub plays a key role in the dissemination of information about DMD clinical trials through the Clinical Trial Finder. This has been designed for patients, caregivers and healthcare professionals to help them better understand the existing and upcoming clinical trials in DMD throughout the UK, including recruitment status at sites and the specific outcome measures and inclusion criteria per trial.

The DMD Hub CRD can also help to facilitate a timely identification of potentially eligible patients. The CRD was established in 2022 in order to provide fair and equitable access to clinical research for patients with DMD. The CRD process works well because of the DMD Hub central coordination and data curation, and the network of DMD Hub sites who have agreed to implement a common process.

Survey responders suggested they would like to see the North Star engaging with, and referring patients to the CRD as a way of identifying additional or out-of-area patients. The DMD Hub proposes that sites should use the CRD to recruit one out-of-area patient for every three patients recruited to a clinical trial, or where they need to recruit additional out-of-area patients to meet recruitment targets. This is a fairer and more transparent system for patients, allowing those living far from clinical trial sites to have equitable access to trials.

Additionally, a Hub and Spoke model for out-of-area patients, where DMD Hub (hub) sites work with North Star (spoke) sites to perform some follow up assessments, was suggested as a valid and beneficial model to reduce capacity issues at hub sites, increasing clinical trial experience at spoke sites and reducing the burden for patients, who then travel less for follow up visits.

The CRD model could be reproduced in other disease areas, such as the Haemophilia Network (26,27), where a network of clinical sites is established.

Recommendations:

Endorse the CRD model as the accepted patient referral pathway for gene therapy trials in the UK for DMD.

Work with pharmaceutical companies bringing gene therapy trials to the UK to develop and implement a hub and spoke model across a network of sites to alleviate capacity, upskill staff and reduce burden on patients.

AAV antibody testing

Clinicians were asked whether they thought AAV antibody testing should be made available in a clinical setting, independent to a clinical trial, to facilitate the consultation with families about eligibility for clinical trials. Most clinicians believed that this would not be beneficial and should remain within the context of recruitment to clinical trials. AAV antibody test results are only valid for a limited period of time, because the patient could seroconvert due to an illness. As such, testing needs to be done as part of the work up for a patient to enter a trial. If testing is done outside of this limited period, it could give families false hope about their potential eligibility for recruitment to a clinical trial, given antibody status can change over time.

Two respondents suggested it should be available independent of a clinical trial but for other purposes. It could be helpful to know from an epidemiological perspective to increase the understanding of antibody levels in different regions or ages, as well as cross reactivity between different AAVs and assays. Having the test clinically available would also potentially stop families paying for independent AAV testing. The pharmaceutical companies running gene therapy clinical trials have explicit specifications for AAV antibody testing, so independent tests are often not relevant, leaving families out of pocket for no benefit. Further education to highlight this to families is needed.

Every effort however should be made to reduce the time for the AAV antibody test results, to avoid patients and families waiting for several days (even weeks in some cases) before confirming whether the child is eligible for a clinical trial. Transparency from the pharmaceutical companies offering gene therapy around their AAV testing and standardisation of tests would help in managing patients' expectations.

It was suggested that the consent process for gene therapy clinical trials should be reviewed, and a 'split consent' process considered. If initially a patient is consented for an AAV antibody test, and if negative, fully consented for the clinical trial, this would reduce the burden on clinicians and manage expectations for patients. It takes several hours to understand the processes of a clinical trial and provide full consent/assent, and the patient can subsequently fail the AAV screening process.

Recommendations:

Pharmaceutical companies should streamline the process for AAV antibody testing, to shorten the turnaround time for results.

Clinicians and pharmaceutical companies to review and discuss the consent process for gene therapy clinical trials. Consider establishing a 'split consent' process.

Existing infrastructure in the UK

Infrastructure refers to the staff, resources, and space sites have available to either refer or accept patients that have been referred for gene therapy clinical trials. Without the appropriate infrastructure this would not be possible.

Most sites surveyed have the appropriate licences and accreditations to deliver gene therapy clinical trials. There is not a one size fits all answer for where investment would be most effective in improving infrastructure across gene therapy clinical trial sites. Investment should be overseen by people with the knowledge at individual site level, who understands the requirements specific to their team.

Fair and equitable recruitment: who makes the decision?

There is currently a variable approach to screening patients for inclusion in clinical trials, with most sites suggesting that they randomly select a patient from a clinically eligible cohort taken from their clinic lists. The capacity of the patient to comply with what is required for a specific trial is also considered, such as the likely ability to perform required assessments, engagement and likelihood of reliable attendance.

Whilst all sites that were surveyed are able to refer patients to clinical trials outside of their own NHS Trust site, only half said they have a specific process in place, of which the methods varied. Clinicians are willing to discuss patients' interest in clinical trials during their clinic appointments. They go through the eligibility criteria of a trial and whether they think the patient would be suitable, as well as explaining the commitments of taking part in a trial. The DMD Hub clinical trial finder can be used to facilitate these discussions, informing patients and clinicians of ongoing clinical trials in the UK, including key eligibility criteria. Clinician's signpost how to get in contact with trial sites or offer to get in contact on the patients behalf, however, most are now referring patients to the CRD.

The CRD has been developed in order to provide a fair and equitable process for patients accessing clinical research. This reduces the burden on individual clinics; they no longer need to maintain lists of out of area patients interested in clinical trials at their site, as the site can refer the patients to the CRD directly. Patients and families will no longer have to spend time trying to contact multiple clinical trial sites across the UK to see if there is a place available for them. This also provides patients with the possibility of being considered for all open clinical trials they are interested in.

Where a trial has many potential participants, some survey participants noted they are committed to recruiting one patient from the CRD to every two local patients in future trials. This provides a consistent and transparent approach for patients and increases the likelihood of patients in areas not well covered by expert neuromuscular care to still access research.

There is still an issue with being able to refer patients outside of the UK, where information is more difficult to access about the trial and how safe and reasonable it would be for the patient. There is no clear method or process of how to share information outside of the NHS Framework.

Recommendation:

Encourage clinicians at sites to adopt a fair and equitable process for selecting non-local patients for recruitment into clinical trial, such as the CRD.

Promote the use of the DMD Hub clinical trial finder to patients and clinicians to find information about ongoing clinical trials which may not run at their clinical care site.

Clear processes should be established so clinicians feel reassured the out of area patients will comply and that it will not result in additional work.

Follow up: what happens after a trial has ended

While taking part in a clinical trial, the trial site is responsible for trial related procedures, whilst the patient's standard care remains with the referring site. Good and timely communication between the trial site and the referring site is critical during this time, and flexibility in responsibilities should be considered to reduce the burden for the patient. It is also extremely important that the family have clear guidance of who to contact when, particularly in an emergency.

After the trial has ended, there should also be clear communication about how to transition the patients care back to the local site and who is responsible for the long-term follow up or data collection outside a clinical trial. Cost implications will need to be carefully discussed. Any additional costs incurred by sites in addition to the provision of care (e.g. to increase capacity or staff time to perform follow up data collection) or patients expenses (e.g. for additional travel and visits) should be provided by the sponsor.

The post-trial long-term follow-up, monitoring and data collection highlight the importance of ensuring that education and training regarding monitoring of efficacy and safety outcomes as well as management of potential side effects are disseminated widely and not limited to clinical trial sites.

The majority of sites have been involved in an early access or compassionate programme such as the Early Access to Medicine Scheme (EAMS), following the end of a clinical trial. EAMS, established by the MHRA, aims to give patients with life threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need.

Most sites found the EAMS process challenging. Whilst funding is provided (from the company) for the drug, there is a lack of funding to sustain the delivery of the medicine under EAMS, which can require activities above the routine standard of care, such as nursing support, additional safety monitoring and reporting. Furthermore, the cost of preparing and supervising drug preparation is taken up by NHS pharmacy, which can be unsustainable. It is the site's responsibility (trial site and/or referring clinical site) to provide educational materials and further information for patients and

families, further increasing their burden. The lack of consistency of these variables can lead to unnecessary additional stress and anxiety for patients and families, as well as a delay in accessing vital medical interventions and/or appropriate monitoring after a trial has ended. Due to the highly controlled advance therapy monitoring required for administration of gene therapy medicinal products it may be unlikely that it will be available through an EAMS, however, sites previous experience have been included for completeness of a site's experiences. Moreover, it highlights the importance to carefully consider the implications of post-trial long term safety and efficacy monitoring and reporting, as well as training needs on clinical services and the cost associated with this.

The priority for sites is to offer the opportunity to patients to take part in a clinical trial. However, they also indicated that the lack of clear exit strategies, plans for long-term follow up and data collection after clinical trials, may have an impact on their decision to participate in the future. Additional costs and capacity should be carefully considered.

The comments from these surveys highlight the critical need to upskill staff and increase the capacity of sites across the UK, not just those taking part in clinical trials, to ensure a consistent and equitable approach to clinical trial access and long-term monitoring and follow up, no matter where the patient is based.

Recommendations:

Good and timely communication between the trial site and the referring site is critical, and flexibility in responsibilities should be considered to reduce the burden for the patient during the study and for the post-trial long-term patient monitoring.

During the study, a communication plan should be developed as part of the referral process to clearly establish role and responsibilities according to the clinical trial and care requirements. This should be clearly discussed with the family. An individual referral plan should be developed at the end of the study for the long-term patient care monitoring; training and educational needs as well as cost implication and family burden should be considered in the development of the plan.

Coordination and communication of referrals

Clinicians that had experience of using the CRD (five out of six) reported that they mostly make patients aware and discuss it with them during clinic. Newly diagnosed patients and those interested in taking part in clinical research should be informed of the purpose of the CRD and reminded at follow up appointments. Some clinicians noted they have flyers available in clinic and have previously sent email and postal information sheets to their entire clinic list to inform patients about the CRD. Patient organisations, in particular Duchenne UK, have also played a critical role in the dissemination of this information, through newsletters, email, social media, and information provided on their website.

Clinicians believe that the CRD has had a positive effect on their ability to refer or accept patients for clinical trials. It allows more effective identification of potentially eligible patients, enabling them to

fulfil recruitment targets. It also increases equity of access for patients and reduces the burden on clinicians receiving contact from families about their potential participation in a trial.

Patients are also able to search for upcoming clinical trials through the DMD Hub Clinical Trial Finder (https://dmdhub.org/clinical-trial-finder). Every trial listed on this site includes information on which sites are running the trial, recruitment status at the sites, outcome measures, inclusion criteria and an easy-to-understand lay summary.

Sites were asked if planning for post treatment patient care (including post-trial activities and early access programs) effects their decision to refer/accept patients for clinical trials. While clinicians noted that the patient being able to take part in research is the priority, there are implications on a centres' capacity to take on referrals, which is potentially influenced by funding available. Clear communication and defined exit strategies between sites and sponsors need to be put in place prior to the commencement of the trial to support post-trial activities and before starting an EAMS. Funding should also be made available to the patients referring local site (not the clinical trial site) if additional care will be required because of this.

Recommendation:

Clear communication and defined exit strategies between sites and sponsors need to be put in place prior to the commencement of the trial to support post-trial activities. This should include addressing educational and training needs, as well as capacity and cost implications.

Patient expectation

Patient expectations should be carefully managed, before and throughout the clinical trial, to ensure they are fully aware of the trial procedures and timelines, as well as the potential benefits and risks of taking part in a gene therapy clinical trial.

There is a combined responsibility between clinicians of both the local and trial site, patient organisations and regulators in managing patient expectations, and ensuring there is adequate and quality information available for patients and their families about current and upcoming clinical trials.

The patient's local site should be able to inform their patients about the referral process and pathways. The clinical trial site should be best placed in explaining selection and acceptance criteria; however, all sites should have access to information to allow them to understand the processes to ensure a clear unified message is passed to the patient community. Time and capacity within clinics can restrict their ability to discuss upcoming clinical trials. However, it should be in the standards of care that clinicians discuss potential participation in clinical trials with patients, ideally from shortly after diagnosis. The DMD Hub clinical trial finder can be used to facilitate discussions about clinical trials, and by families to pro-actively identify trials they are interested in to discuss during clinic.

Patient organisations and the DMD Hub could play an important role in ensuring that the decision-making processes around patient referral, selection and acceptance are disseminated across the patient and clinical communities, as well as clinical trial sites. They also have a responsibility to keep the patient community updated about upcoming trials, such as through the Clinical Trial Finder. Shared resources in raising awareness of clinical trials can be helpful in easing the burden on time in clinics. Resources will need to be tailored to the age range of the patient group taking part in the trial. Appropriate educational materials will be different for a 4-year-old compared to what is appropriate for a teenager, for example.

Regulators, such as the MHRA, should be involved in defining how the communication about clinical trials is passed to the patient community as well as in the communication about the process to identify, select and accept treating sites and patients.

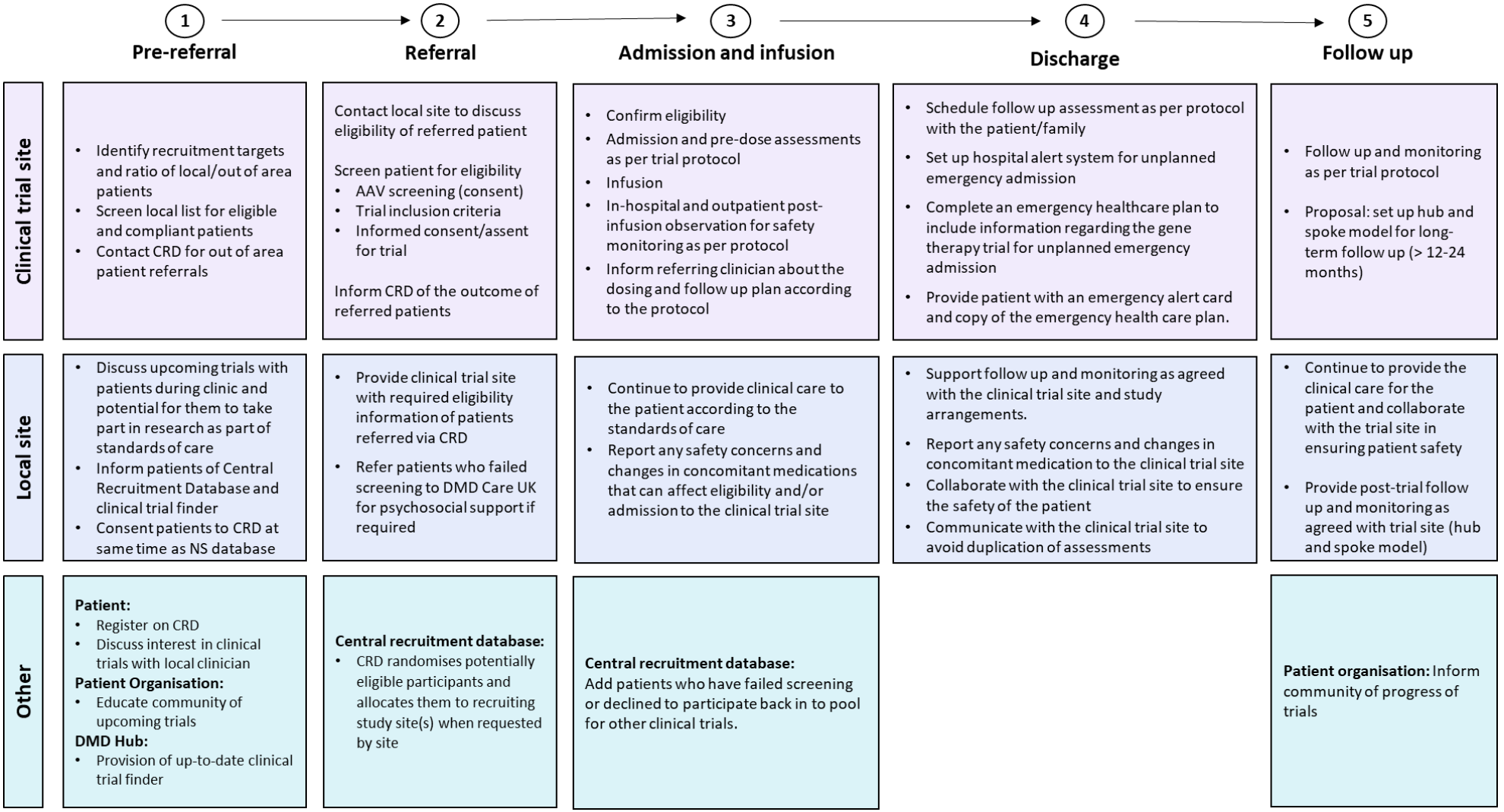
Recommendation:

Responsibility for managing patient expectations should be shared between clinicians at local referring sites and clinical trial sites as well as the regulators and patient organisations. Resources and communication should be harmonised and the DMD Hub website can act as a central repository for information for clinicians as well as patients.

Proposed Patient Referral Pathway for Clinical Trials

The results from this section have guided the proposed patient referral pathway shown in Figure 2. Responsibilities are clearly labelled by clinical trial site, patient's local (referring) site and other, which includes patient organisations and the CRD.

Figure 2: Proposed patient referral pathway for gene therapy clinical trials.



Licenced product patient referral pathway

To date there are a limited number of licensed (Market Authorised) products to treat DMD. Ataluren is approved in the UK and European Union. Eteplirsen, Golodirsen, Casimirsen, Viltolarsen and now ELEVIDYS are approved in US. However, the new era of gene therapy clinical trials brings with it a new level of expectation and hope from the DMD community for the development of an effective treatment.

With one approved gene therapy product (Zolgensma) in SMA available in the UK and several in the pipeline for DMD, it is important to discuss and agree how patients and their families, sites, industry and regulators can be assured there will be an appropriate and agreed referral process in place to help ensure fair, equitable and coordinated access to treatment.

These responses were taken in the months prior to the FDA accelerated approval of ELEVIDYS in the USA. ELEVIDYS is the first and only gene therapy approved to treat DMD at the time of writing. It has received accelerated approval for use in a limited patient cohort in the US (four to five years old boys with DMD), but it is not currently available in the EU and UK outside a clinical trial.

Workforce planning

NHSE have set up a national multi-disciplinary team (MDT) and a referral portal that has supported referrals for gene therapy in SMA at national level. For non-commissioned referring sites, this has worked well, and they have received quick responses as users.

However, survey responses indicated that investment to improve capacity and infrastructure for the delivery of gene therapy by NHSE was slow, and clinicians from commissioned sites noted that they were dosing patients for some time before this support was received at their Trust. Key roles were not able to be trained promptly, and admin support was not provided as part of the set-up despite the referral pathway and timed treatment requiring a lot of coordination, stretching clinical capacity further. Furthermore, safety monitoring at the patient's local referring site is not currently supported.

In general, most sites believe that the workforce planning and forecasting currently in place will not be effective in enabling referrals to be made in a timely manner for DMD. While the referral pathway for gene therapy in SMA is adequate, the larger numbers of DMD patients present a potential problem for capacity in both the referring and commissioned sites.

Recommendation:

A referral portal for DMD gene therapy licensed products, similar to that set up for SMA gene therapy, Zolgensma, would be welcomed but infrastructure and increased capacity would need to be available in a timely manner to ensure timely access to therapy and to avoid capacity issues at sites, as was experienced with SMA.

Commissioning of sites

The majority of sites believe that the number of UK sites (four in total) commissioned to deliver gene therapy in SMA is appropriate to manage the national SMA caseload. The initial backlog of prevalent cases were dealt with in a timely manner and the four sites now commissioned are able to quickly treat incident cases.

The incidence of DMD and current prevalent population is higher than the SMA caseload. Consequently, a higher number of sites will need to be commissioned to deliver gene therapy in DMD, although the exact number will depend on the age and eligibility of patients approved to receive the treatment. Those surveyed believed that approximately eight commissioned sites will be needed to meet the clinical demand in a timely manner and manage the impact of the increased workload on other service and centre capacity. The geographical location of sites should also be considered to reduce the burden of travel for patients (see figure one for estimated spread of prevalent population at DMD Hub sites).

A national MDT should be established to aid in the referrals for gene therapy in DMD. Based on the positive experience, the role of a national DMD gene therapy MDT could be similar to the role of the SMA national MDT on triage, prioritising referrals and checking eligibility criteria. Key opinion leaders and principal investigators from the gene therapy clinical trials (if different than one of the selected commissioned sites) and the clinician from each commissioned site should be invited to be a part of the national MDT to provide expert guidance with the initial processes.

A national safety task force could also be established to develop a standardised national protocol for the monitoring of long-term safety and efficacy of approved gene therapies. It could also advise on management of side effects (working in close collaboration with a national MDT and local safety task forces). This could allow for learning from the safety profiles of other approved medicines in other disease areas. The national safety task force would need to be multi-disciplinary and include specialists in a range of aspects of safety monitoring, including neuromuscular disease specialists, nephrologists, hepatologists, immunologists, haematologists and pharmacists.

There is broad support for not duplicating efforts and using the SMA gene therapy referral pathway as a baseline for the development of a pathway in DMD, with some amendments and improvements considered due to lessons learnt and the higher prevalent population. The SMA pathway itself has evolved with the growing guidance and information available, so effective communication between sites and with the MDT will be critical in ensuring a consistent approach across the UK. The online referral portal used for SMA gene therapy worked well and it would be sensible to use the same portal adapted for DMD, so that it may be readily available.

All sites surveyed submitted a bid to become a commissioned site for SMA, with three of the six interviewed being successful. All sites found the submission process challenging as it required a significant investment of time, including extensive multidisciplinary discussion and development of a service design that, when operationalised, would align with the site's strategy for advanced therapy delivery. For commissioned sites, the process was useful in planning and implementation of the service. Survey participants suggested that it was not clear how answers would be scored and what was required by particular questions. There was some debate in the clinical community around the clinical trial sites with strong academic expertise not being selected to be commissioned sites. More

transparency of the selection process and criteria by NHS England would be favoured for the DMD gene therapy commissioned site selection process.

Recommendations:

NHSE to endorse the development of a proposed, nationally agreed referral pathway for sites to utilise and include in their applications to become a commissioned site.

A national MDT should be established to aid in the referrals for gene therapy in DMD, as well as a national safety task force to monitor the long-term safety profiles of approved gene therapies and advise on the management of side effects.

Education, training and CPD

There are a variety of resources that sites are aware of for education and training around gene therapy medicinal products, however there was no consistency of answers across different sites. Some highlighted the ATTC network as very useful, with their team members attending educational webinars and the institutional readiness toolkit being a valued resource (28). Others mentioned the training provided by the DMD Hub for gene therapy clinical trials, as well as educational events for research nurses and clinical trial coordinators. The British Society for Gene and Cell Therapy (BSGCT) was mentioned, which provides a variety of educational resources for gene therapy more generally, including webinars and an annual conference.

All sites believed that there is not enough training and educational opportunities to ensure staff (including clinical, laboratory, pharmacy, admin etc.) are as knowledgeable as they could be around gene therapy. They also highlighted problems with capacity, meaning staff had limited time to access training. Additional training regarding mechanism of actions, handling, risk and management of expected side effects, appointment requirements in terms of coordination and administrative support would be welcomed.

There is a clear educational need for a range of staff involved in the administration of gene therapy. A sponsor provides mandatory training during a clinical trial, however for a licenced product it depends on the product label to dictate who is responsible for the training. The standardisation of training between clinical trial and licenced product would be of benefit, as well as recognition of transferrable skills between the trial and the clinic. Better signposting of existing resources could also help for a more consistent approach across sites. Reliability of scales used to measure outcome is desirable and could be arranged through existing networks and infrastructure.

Recommendation:

There is an educational need for training of staff involved in gene therapy clinical trials and advanced therapy licenced products. This training should be developed and maintained with up-to-date information about risk and management of side effects, handling, and mechanism of action. Materials are available but need to be better signposted to reach its intended audience.

Number of treatment sites

If gene therapy was approved for treatment in DMD, sites believe they would be able to safely dose one to two patients per month. This is based on sites previous experience in trials as well as licenced gene therapy in SMA; the sites caveated that it may be different depending on eligibility of patients in DMD compared to SMA, as well as time to set-up, capacity and experience of the sites. Clinicians noted that the infusion itself was not the time limiting factor, rather the safety monitoring and follow up that would limit their capacity to treat more patients.

Geographical spread of patients will also need to be considered for site selection, reducing the burden of travel on patients and families (see figure one for estimated geographical spread of population and patient numbers at 11 DMD Hub sites).

Recommendation:

When deciding on the number and location of commissioned sites, NHSE should take into account the prevalent population, geography of sites, experience and capacity of sites to treat a limited number of patients.

Network between referral centre and treatment centre

Three of the sites surveyed are commissioned to deliver gene therapy in SMA (Zolgensma), however, all sites have the appropriate facilities and equipment to deliver licensed gene therapy medicinal products, demonstrating there is infrastructure in the system to deliver more gene therapies if required.

Centres coordinate referrals for Zolgensma through communication with a network of sites close to them geographically. These referrals are then submitted to the national portal to be discussed formally by the MDT (29).

Investment to improve the referral pathway of patients for gene therapy licenced products should have a degree of flexibility to be targeted where needed, whether this be local or national. It is important for funding to be ring fenced specifically for gene therapy patient referrals and not lost in other aspects of clinical service. Specific administrative support should also be provided at the commissioned site to support the coordination of appointments and safety monitoring.

Referrals for gene therapy in DMD should be prioritised at a national level by the MDT based on the determined prioritisation criteria. A better understanding of the approval criteria will help in determining the prioritisation strategy to treat the prevalent population of DMD patients with gene therapy. For example, an approved age or weight range, as well as what is the best expected outcome vs potential side effects, are factors that may affect the prioritisation strategy.

A centralised, national database could be a useful tool to support the prioritisation process by the MDT, providing a real time understanding of the number of potentially eligible patients. This could also inform NHSE decisions on required number of treating sites to ensure a timely referral and delivery of gene therapy to eligible patients. SMA REACH UK (https://smareachuk.org/) has been helpful in understanding this in gene therapy for SMA, working with the national MDT to agree prioritisation criteria. The DMD Hub CRD is currently used to aid clinical trial referrals, and an adapted model could in theory be used in this planning, with consent from the patients for their data to be used in this way.

Recommendation:

A centralised national database which includes potentially eligible DMD patients for gene therapy would be beneficial to support referrals. NHSE would be best placed to support the development of this.

Prioritisation

Most sites think that the prioritisation strategy implemented for licenced gene therapy in SMA was effective for patient referrals. Criteria was agreed at a national network meeting and shared with patient advocacy groups. One site disagreed, highlighting that SMA type 2 is not offered treatment as per NICE and NHSE criteria, despite being available in other countries.

The prioritisation strategy is likely to be different in DMD compared with SMA. This should be guided by clinicians, with support from regulatory authorities to match resources that are available. Once the prioritisation strategy is established, a national MDT would be best placed to make decisions over specific prioritisations in DMD, comprised of infusion centre clinicians, clinical experts in gene therapy and DMD, NHSE and NICE. One participant noted that patient groups could also be present to provide feedback from the community. Once prioritisation criteria are agreed, these should be clearly communicated and available to patients and patient advocacy groups.

AAV antibody testing

In general, sites did not believe that AAV antibody testing should be made available on the NHS ahead of gene therapy being licenced. There is a limited validity window, and the test would need to be repeated prior to administration of treatment to determine the most accurate result.

Currently AAV antibody testing (for SMA patients considered for gene therapy only) is restricted to a few sites in the UK due to contracts with industry, with testing being carried out abroad and a turnaround time of approximately three days. It will be beneficial to implement AAV testing in national laboratories to receive standardised results quickly before or at the time of licensure of a gene therapy product to treat DMD.

Notification of new treatment options

For healthcare professionals, the current communication strategy for new treatment options is varied. It is important that the information available is consistent and reaching all healthcare professionals, to ensure equity of access to all eligible patients.

Existing networks for DMD, including the North Star Clinical Network, DMD Hub as well as DMD Care UK could play an important role in disseminating information and ensuring that all stakeholders, as well as new staff, are reached and that the information is maintained and updated over time.

Further work could be done to try to reach non-neuromuscular specialists (e.g. general paediatricians, general practitioners, cardiologists, hepatologists, and haematologists) to ensure that they are also aware of the fact that there are treatment options. This broadening of education could lead to improved diagnosis, emphasising the importance of early recognition to offer early interventions, and increased awareness of required safety monitoring.

Presentation at national and international conferences can also help to raise awareness of new treatments to a wider audience. Communication through professional organisations could also be considered, such as the British Paediatric Neurology Association (BPNA) and the Royal College of Paediatrics and Child Health (RCPCH).

Recommendation:

Notification of new treatment options needs to be coordinated on a national level. NHSE can advise on how this can reach across multiple healthcare disciplines.

Timelines

Sites expect that if they were commissioned to deliver gene therapy it would take three months at a minimum to set up to treat patients, but likely take longer. Receiving the required support from their NHS Trust/Board and approving a business case to make sure funding are in place to support the programme can take several months. Furthermore, the process to recruit and train staff to deliver the treatment is complex within the NHS and can take some time.

Sites involved in delivering SMA gene therapy stated they were delivering the treatment for some time, at risk, before funding became available to them, adding pressure to their clinical service. One site stated having to use temporary contracts for the service before contracting was complete in order to deliver the therapy quicker to patients. This is not sustainable for sites so should be prevented from happening again.

Once an appropriately resourced referral pathway is in place and appropriate education on the risks and benefits are available to make an informed decision, the process to refer a patient to a commissioned site for gene therapy should be quicker. The lead time will also depend on the staffing levels at both the commissioned and referring sites, the number of sites able to deliver gene therapy and the number of patients in the prevalent population eligible to receive the treatment.

The consensus among clinicians surveyed was that it will be less urgent for DMD patients than it was for SMA patients to receive gene therapy treatment, and so one to three months for referral could

be an appropriate time frame. However, AAV negativity could be compromised in this time, so ideally eligible patients would be treated at the earliest opportunity. A database held and curated by the National MDT would also be beneficial to understand the prevalent population and prioritisation strategy (as discussed above).

Coordination implementation

The clinical lead should coordinate the implementation of a licensed product within their NHS Trust/Board, with the support of different professionals such as business and directorate managers, pharmacy etc. Sharing resources, protocols and best practice between sites, as well as support from the clinical research lead if present within the same centre can be beneficial and save considerable time.

Ring-fencing funding would be of benefit as prioritising a specialised treatment for a relatively small number of patients is not always possible in an integrated care system with other service pressures and limited capacity. Not all sites currently have a clinical care coordinator (or equivalent team member) to support the logistics and communication around planning and delivery of treatment, however it would be best practice to have a dedicated person in this role. This would be critical to reduce the burden to families and optimise referral pathways without adding further pressure to other clinical services.

Recommendation:

Dedicated resources for coordinating and delivering gene therapy should be allocated within a service at a site level. Networks such as the DMD Hub, DMD Care UK and North Star can help to support the development and dissemination of these resources.

Notification of eligible patients

Patients eligible for a newly approved licenced product should be efficiently and effectively notified of this development. It is important that there is a clear and consistent message delivered to the community, which could be from a variety of trusted sources, such as within clinics, NHSE and patient organisations.

A patient information day would help to inform patients and families about the developments of the licencing process and allow them to ask questions in anticipation of approval. Treatment options and eligibility criteria for gene therapy should be easily accessible through a variety of sources, including NHSE, the DMD Hub and patient organisation websites. Webinars, frequently asked questions and leaflets should be developed in order to deliver this, as well as managing expectations. This would require coordination, resourcing and funding.

Clinicians should also reach out individually to potentially eligible patients, inviting them to clinic to discuss their options face to face. With enough notice from NHSE, clinicians can plan in advance when to invite patients for clinic appointments to discuss this. Depending on the licenced product criteria and the prevalent population, support and may be required to avoid impact on clinical care to other patients.

Recommendation:

Deliver timely information to patients around eligibility on a person level (clinic, clinicians) and on a community level via webinars and patient information days (NHSE and patient organisations)

Follow-on planning

Close communication between the referring and treatment site is essential to ensure a safe and suitable follow-on plan for the patient. A virtual meeting before the patient's discharge should be held between the infusion site, referring site and local community paediatrician to set out lines of responsibility and points of contact for families and health care professionals. This agreement should be formalised in a discharge letter that can be shared with the patient. An emergency healthcare plan should be developed and shared with all clinicians and the patient prior to discharge.

Sites agree that the short-term safety monitoring post infusion and adverse events would be the responsibility of the infusing site, however specific arrangements could be made to ease the burden on the patient (for example, safety blood tests could be performed at the patient's local site and community paediatrician, but reviewed by the infusion site). The sites must understand and agree on the importance of timed communication between the sites on any concern during this period. Education around safety risks and monitoring requirements for staff outside of the infusion site will be critical in ensuring equitable care. The long-term safety and efficacy monitoring will be the responsibility of the referring site.

Patient expectations

There should be a national communication strategy agreed to coordinate communication, including who should communicate to patients about what and manage expectations around time to access, efficacy and safety. This will ensure that a harmonised message is given to patients, and that information is accessible through multiple channels. This strategy should be clinician led, but supported by patient organisations, NHSE and NICE.

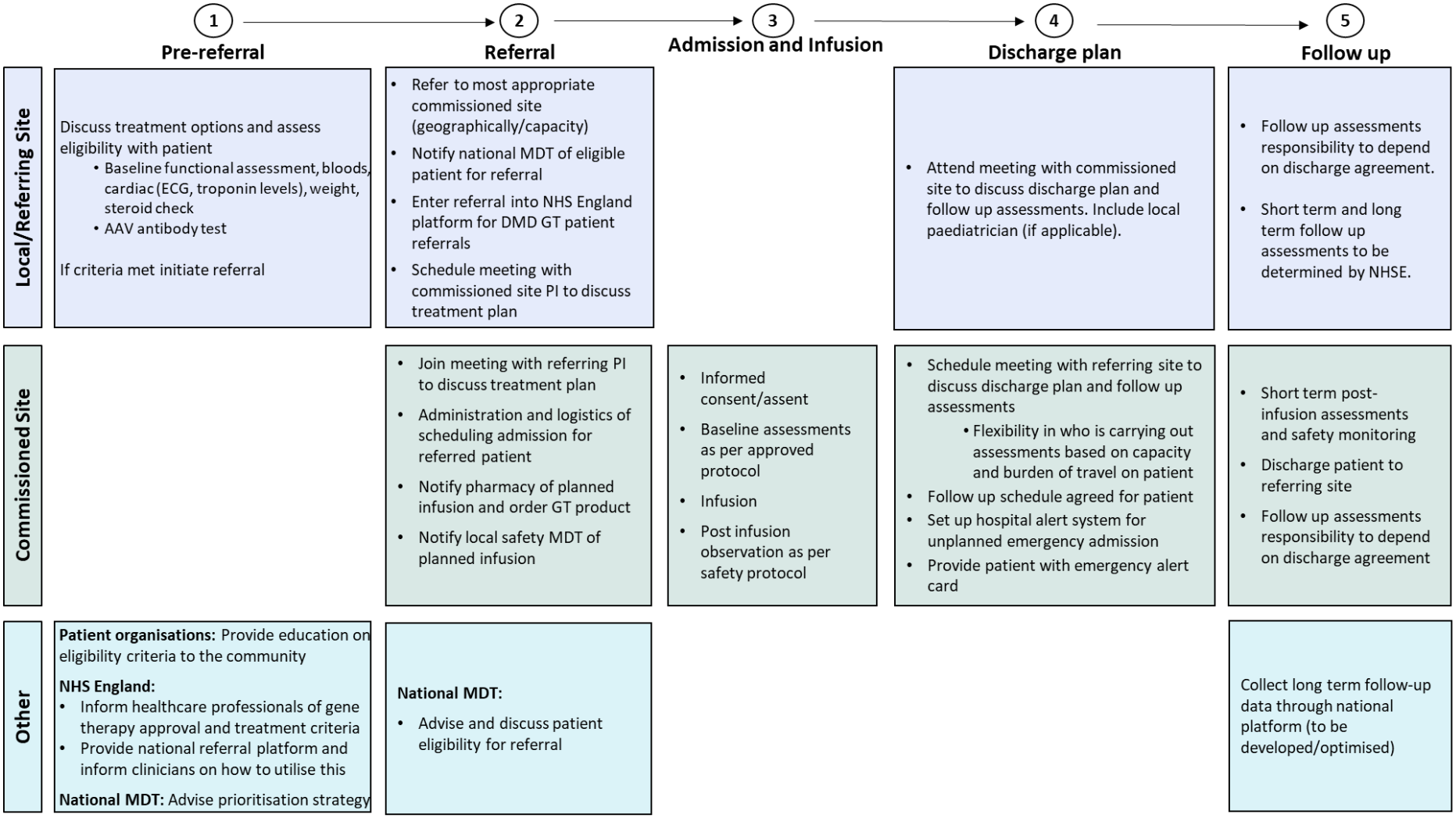
Education and training around gene therapy is therefore critical to empower clinicians with less direct experience with gene therapy to access and provide accurate information around expectations and accessibility.

The patient referral pathway to access gene therapy must be made clear to patients to reassure them they are not missing the opportunity to access and avoid families contacting several centres at the same time.

Proposed patient referral pathway for gene therapy as a licensed product

The results from this section have guided the proposed patient referral pathway shown in Figure 3. Responsibilities are clearly labelled by patients local (referring) site, the commissioned site delivering the gene therapy and other, which includes roles such as patient organisations and a proposed national MDT.

Figure 3: Proposed patient referral pathway for gene therapy as a licenced product.



Discussion

The number of clinical trials for advanced therapy medicinal products, such as gene therapies, are increasing in the UK (31). The advancement of gene therapy clinical trials in DMD, and the recent accelerated approval of a gene therapy product for use in a limited cohort of DMD patients in the United States, indicates an immediate need to discuss gene therapy and the referral processes for DMD patients in the UK.

According to the Association of the British Pharmaceutical Industry (ABPI) there has been a 44% decline in the number of patients enrolled onto commercially led studies supported by the NIHR between 2017 and 2022 (30). However, this decline has not been seen in the number of DMD patients taking recruited to clinical trials over the same period. The DMD Hub, funded by Duchenne UK, is a unique model that is able to support access to clinical trials through a network of clinical trial sites across the UK, and key investment in capacity, infrastructure, and education.

Clinical research and clinical trials should be seen as an integral part of patient care. The NHS aims to embed research within its standards of care, to provide evidence to transform services and improve quality of life and outcomes for patients (32). However, with funding and capacity continually stretched within the NHS, investment is often directed to clinical care rather than clinical research; resulting in researchers in academia, NHS and industry feeling as through research is not a priority for the NHS (33).

The comments from these surveys and interviews highlight the critical need to expand the UK's ability to deliver safe and effective clinical trials; by building site capacity and upskilling staff not routinely involved in clinical trials. With an increase in gene therapy clinical trials expected in the UK, it is not sustainable to rely on patient organisations and charities to fund the expected increase in capacity.

Gene therapy clinical trials come with a high risk and requires support from skilled multi-disciplinary teams, including pharmacy, cardiology etc. Capacity for gene therapy clinical trials therefore goes further than the research clinic. By improving skills in staff beyond clinical research teams and raising awareness of advanced therapy medicinal products such as gene therapy, safety monitoring could be safely and effectively managed between referring and treatment sites post infusion as part of a hub and spoke model.

Further discussion is needed about long-term follow up from gene therapy clinical trials, including who is responsible for reporting and who owns the data. While safety monitoring data and patient outcomes will be collected as part of the trial, general standards of care will also be collected concurrently, as well as long after the trial has finished. Long-term data will be critical in understanding the effectiveness of gene therapy over a longer period, but funding will be needed to continue this data collection clinically. The UK is in a unique position with existing DMD focused infrastructures in place to help this, including clinical networks, national patient organisations supportive in collecting and sharing of patient data and experiences in other disease areas (e.g. SMA REACH UK). Optimisation of this existing infrastructure, and funding for implementation and data entry would provide reliable data to evaluate the long-term safety and efficacy of new therapeutic approaches for DMD.

The current process for DMD patients accessing research, including gene therapy clinical trials, is variable. The DMD Hub CRD has created a model for inclusive and equitable access to clinical trials and aims to reduce the burden on sites and patients facilitating access for out of area patients to clinical trials. To ensure all patients are informed of the CRD process, the DMD Hub engages with patient organisations and North Star Clinical Network to ensure the reach is as broad as possible. At the point of diagnosis, every patient should be offered the possibility to participate in research. If healthcare professionals were able to consent patients to register on the CRD, with the CRD following up to complete the patient's details, this could facilitate reaching and informing families who are less engaged.

There is a great deal for patients and caregivers to consider when deciding to take part in a clinical trial, including weighing the risks and benefits. Guidance and education about gene therapy and clinical trials more widely is needed for the patient community, so they can make an informed decision. Furthermore, with ELEVIDYS being recently approved in the US, there may be a decision point in the future of whether UK patients choose a licensed product or continue with research studies. Education will also need to be widely available for healthcare professionals, to ensure research is integrated into patient care from the point of diagnosis, as well as a consistent and informed message is passed on to patients and expectations are well managed. Survey responses highlighted that while educational materials are available (e.g. resources and webinars provided by iMATCH), but these are not reaching their entire intended audience.

It is difficult to set realistic expectations for patients without all the data being yet available, such as factors that might exclude them from treatment. For instance, the Sarepta trials for ELEVIDYS were in DMD patients aged four to seven, but it was only approved by the FDA in the first instance for ages four to five. Transparency and clear communication from NHS commissioners to sites prior to approval would help in allowing clinicians to manage expectations of patients when a product is approved. The responsibility of managing patient expectations should be shared by regulators, patient organisations, and healthcare beyond the commissioned centres, such as primary or secondary care.

A bottleneck for patients receiving gene therapy once approved is the funding for the delivery of treatment through the NHS. Better communication from regulators and funding opportunities to increase capacity prior to licencing could be beneficial to speeding up this process, allowing patients to access treatments earlier.

All clinicians agreed that a national MDT, similar to the one used for SMA, would be beneficial to review and coordinate gene therapy referrals in DMD, as well as a national referral platform provided by NHSE. Regulators and NHSE could advise on the set up of the MDT prior to approval to speed up the process. If set up prior to approval, key opinion leaders could provide insight to the number of national referrals and therefore advise on infrastructure requirements, anticipate capacity issues affecting the timelines of referrals and delivery. Recommendations for these can be found within this document. The MDT would also be best placed to advise on the prioritisation strategy for treating patients with gene therapy. Similarly to the SMA field, should there be more than one product approved, a clinical panel of expert professionals and NHSE may be necessary as well that will feed into the national MDT.

The cost of gene therapy in DMD could pose as a potential barrier to approval for use in the NHS. ELEVIDYS has a price of US$3.2 million per dose in the US (34), although the price will likely be

different if approved for use in the UK. It is expected that the use of gene therapy should reduce the costs for the NHS over time, although it is still likely that the patient will require a combination of other medications. Zolgensma was listed as the most expensive drug in the world at the time of approval at £1.79 million per dose (35) but shows remarkable improvement of patients with SMA treated pre-symptomatically.

Conclusion

It was widely agreed that there is an efficient referral process in place for DMD clinical trials, via the DMD Hub CRD, which can be effectively implemented for gene therapy trials and that for licenced products the pathways set up for SMA are a good starting point that would require some improvements.

A set of recommendations for improved, standardised future practice is proposed, as well as referral pathways for gene therapy clinical trials and licenced products for DMD. These are to be adopted by the DMD community and promoted as best practice by NHSE.

Recommendations

Clinical trials patient referral pathway

- NHS England (NHSE), and devolved equivalents, should play a key role in ensuring that adequate and sustainable infrastructures are in place for effective patient referrals to gene therapy clinical trials.
- Providing specific gene therapy training and education opportunities, and supporting accessibility, doctors and other healthcare professionals could be better attracted to the specialty of neuromuscular disorders. This would benefit DMD as well as other disease areas where gene therapy is in development as a potential therapeutic approach.
- Consider where additional clinical trials sites for future gene therapy trials should be located geographically to ensure equitable access to clinical trials. Explore resources and facilities in areas currently not covered for the delivery of clinical trials (e.g. Wales, Northern Ireland) and invest in developing infrastructures to deliver clinical trials (and approved medical products) in the future.
- Endorse the CRD model as the accepted patient referral pathway for gene therapy trials in the UK for DMD.
- Work with pharmaceutical companies bringing gene therapy trials to the UK to develop and implement a hub and spoke model across a network of sites to alleviate capacity, upskill staff and reduce burden on patients.
- Pharmaceutical companies should streamline the process for AAV antibody testing, to shorten the turnaround time for results.
- Clinicians and pharmaceutical companies to review and discuss the consent process for gene therapy clinical trials. Consider establishing a 'split consent' process.
- Encourage clinicians at sites to adopt a fair and equitable process for selecting non-local patients for recruitment into clinical trial, such as the CRD.
- Encourage the use of the DMD Hub clinical trial finder to patients and clinicians to find information about ongoing clinical trials which may not run at their clinical care site.
- Clear processes should be established so clinicians feel reassured the out of area patients will comply and that it will not result in additional work.
- Good and timely communication between the trial site and the referring site is critical, and flexibility in responsibilities should be considered to reduce the burden for the patient during the study and for the post-trial long-term patient monitoring.
- During the study, a communication plan should be developed as part of the referral process to clearly establish role and responsibilities according to the clinical trial and care requirements. This should be clearly discussed with the family. An individual referral plan should be developed at the end of the study for the long-term patient care monitoring; training and educational needs as well as cost implication and family burden should be considered in the development of the plan.
- Clear communication and defined exit strategies between sites and sponsors need to be put in place prior to the commencement of the trial to support post-trial activities. This should include addressing educational and training needs, as well as capacity and cost implications.

- Responsibility for managing patient expectations should be shared between clinicians at local referring sites and clinical trial sites as well as the regulators and patient organisations. Resources and communication should be harmonised and the DMD Hub website can act as a central repository for information for clinicians as well as patients.

Licenced products patient referral pathway

- A referral portal for DMD gene therapy licensed products, similar to that set up for SMA gene therapy, Zolgensma, would be welcomed but infrastructure and increased capacity would need to be available in a timely manner to ensure timely access to therapy and to avoid capacity issues at sites, as was experienced with SMA.
- NHSE to endorse the development of a proposed, nationally agreed referral pathway for sites to utilise and include in their applications to become a commissioned site.
- A national MDT should be established to aid in the referrals for gene therapy in DMD, as well as a national safety task force to monitor the long-term safety profiles of approved gene therapies and advise on the management of side effects.
- There is an educational need for training of staff involved in gene therapy clinical trials and advanced therapy licenced products. This training should be developed and maintained with up-to-date information about risk and management of side effects, handling, and mechanism of action. Materials are available but need to be better signposted to reach its intended audience.
- When deciding on the number and location of commissioned sites, NHSE should take into account the prevalent population, geography of sites, experience and capacity of sites to treat a limited number of patients.
- A centralised national database which includes potentially eligible DMD patients for gene therapy would be beneficial to support referrals. NHSE would be best placed to support the development of this.
- Notification of new treatment options needs to be coordinated on a national level. NHSE can advise on how this can reach across multiple healthcare disciplines.
- Dedicated resources for coordinating and delivering gene therapy should be allocated within a service at a site level. Networks such as the DMD Hub, DMD Care UK and North Star can help to support the development and dissemination of these resources.
- Deliver timely information to patients around eligibility on a person level (clinic, clinicians) and on a community level via webinars and patient information days (NHSE and patient organisations)

References

1. Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K. Life expectancy in Duchenne muscular dystrophy: reproduced individual patient data meta-analysis. Neurology. 2021;97(23):e2304–14.
2. Aartsma-Rus A, Ginjaar IB, Bushby K. The importance of genetic diagnosis for Duchenne muscular dystrophy. J Med Genet. 2016;53(3):145–51.
3. Crisafulli S, Sultana J, Fontana A, Salvo F, Messina S, Trifirò G. Global epidemiology of Duchenne muscular dystrophy: an updated systematic review and meta-analysis. Orphanet J Rare Dis. 2020;15:1–20.
4. Lim KRQ, Sheri N, Nguyen Q, Yokota T. Cardiac involvement in dystrophin-deficient females: current understanding and implications for the treatment of dystrophinopathies. Genes (Basel). 2020;11(7):765.
5. Soltanzadeh P, Friez MJ, Dunn D, von Niederhausern A, Gurvich OL, Swoboda KJ, et al. Clinical and genetic characterization of manifesting carriers of DMD mutations. Neuromuscul Disord. 2010;20(8):499–504.
6. van Ruiten HJA, Straub V, Bushby K, Guglieri M. Improving recognition of Duchenne muscular dystrophy: a retrospective case note review. Arch Dis Child. 2014;99(12):1074–7.
7. Mercuri E, Bönnemann CG, Muntoni F. Muscular dystrophies. Lancet. 2019;394(10213):2025–38.
8. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Brumbaugh D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018;17(3):251–67.
9. Birnkrant DJ, Bushby K, Bann CM, Alman BA, Apkon SD, Blackwell A, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018;17(4):347–61.
10. Birnkrant DJ, Bushby K, Bann CM, Apkon SD, Blackwell A, Colvin MK, et al. Diagnosis and management of Duchenne muscular dystrophy, part 3: primary care, emergency management, psychosocial care, and transitions of care across the lifespan. Lancet Neurol. 2018;17(5):445–55.
11. Guglieri M, Bushby K, McDermott MP, Hart KA, Tawil R, Martens WB, et al. Effect of different corticosteroid dosing regimens on clinical outcomes in boys with Duchenne muscular dystrophy: a randomized clinical trial. Jama. 2022;327(15):1456–68.
12. McDonald CM, Henricson EK, Abresch RT, Duong T, Joyce NC, Hu F, et al. Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. Lancet. 2018;391(10119):451–61.
13. Duan D, Goemans N, Takeda S, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. Nat Rev Dis Prim. 2021;7(1):13.
14. Berling E, Nicolle R, Laforêt P, Ronzitti G. Gene therapy review: Duchenne muscular dystrophy case study. Rev Neurol (Paris). 2022;
15. Wang D, Tai PWL, Gao G. Adeno-associated virus vector as a platform for gene therapy delivery. Nat Rev Drug Discov. 2019;18(5):358–78.
16. England SB, Nicholson LVB, Johnson MA, Forrest SM, Love DR, Zubrzycka-Gaarn EE, et al. Very mild muscular dystrophy associated with the deletion of 46% of dystrophin. Nature.

1990;343(6254):180–2.

17. Solid Biosciences Inc. Microdystrophin Gene Transfer Study in Adolescents and Children With DMD (IGNITE DMD) [Internet]. ClinicalTrials.gov; 2023. Available from: https://clinicaltrials.gov/study/NCT03368742

18. Genethon. Microdystrophin (GNT0004) Gene Therapy Clinical Trial in Duchenne Muscular Dystrophy. A phase I/II/III study with a dose determination part followed by an efficacy and safety evaluation, quadruple blind placebo-controlled part and then by a long term safe [Internet]. ClinicalTrialsRegister.EU; 2023. Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-002093-27/FR

19. Pfizer. Study to Evaluate the Safety and Efficacy of PF-06939926 for the Treatment of Duchenne Muscular Dystrophy [Internet]. ClinicalTrials.gov; 2023. Available from: https://www.clinicaltrials.gov/study/NCT04281485

20. Sarepta Therapeutics Inc. A Gene Transfer Therapy Study to Evaluate the Safety and Efficacy of SRP-9001 (Delandistrogene Moxeparvovec) in Participants With Duchenne Muscular Dystrophy (DMD) (EMBARK) [Internet]. ClinicalTrials.gov; 2023. Available from: https://www.clinicaltrials.gov/study/NCT05096221

21. Lek A, Wong B, Keeler A, Blackwood M, Ma K, Huang S, et al. Unexpected Death of a Duchenne Muscular Dystrophy Patient in an N-of-1 Trial of rAAV9-delivered CRISPR-transactivator. medRxiv. 2023;2005–23.

22. Philippidis A. After patient death, FDA places hold on Pfizer Duchenne muscular dystrophy gene therapy trial. Hum Gene Ther. 2022;33(3–4):111–5.

23. Food and Drug Administration. FDA Approves First Gene Therapy for Treatment of Certain Patients with Duchenne Muscular Dystrophy [Internet]. FDA.gov; 2023. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treatment-certain-patients-duchenne-muscular-dystrophy

24. Gowda V, Wraige E, Ong M, Atherton M, Majumdar A, Marco SS, et al. Real-world experience of gene therapy with onasemnogene-abeparvovec (Zolgensma®) for patients with SMA-type1 in UK. BMJ Publishing Group Ltd; 2022.

25. Advanced Therapy Treatment Centres. Innovate Manchester Advanced Therapy Centre Hub [Internet]. 2023. Available from: https://www.theattcnetwork.co.uk/centres/imatch

26. United Kingdom Haemophilia Centres Doctors' Organisation. United Kingdom Haemophilia Centres Doctors' Organisation [Internet]. 2023. Available from: https://www.ukhcdo.org/

27. European Association for Haemophilia and Allied Disorders. European Association for Haemophilia and Allied Disorders [Internet]. 2023. Available from: http://www.eahad.org

28. E-learning for Healthcare NHSE. Advanced Therapy Medicinal Products programme [Internet]. 2023. Available from: https://www.e-lfh.org.uk/programmes/advanced-therapy-medicinal-products/

29. Signpost Healthcare. NHS England: Zolgensma gene therapy referral pathway [Internet]. Available from: https://www.signpost.healthcare/zolgensma-referral-pathway-england

30. The Association of the British Pharmaceutical Industry. Rescuing patient access to industry clinical trials in the UK [Internet]. 2022. Available from: https://www.abpi.org.uk/publications/rescuing-the-uk-industry-clinical-trials/

31. Cell and Gene Therapy Catapult. Clinical trials database [Internet]. 2022 [cited 2023 Aug 2]. Available from: https://ct.catapult.org.uk/resources/clinical-trials-database

32. NHS. Embedding research in the NHS [Internet]. Available from: https://www.england.nhs.uk/aac/what-we-do/embedding-research-in-the-nhs/

33. O'Shaughnessy Report. Commercial clinical trials in the UK: the Lord O'Shaughnessy review - final report [Internet]. Department for Science Innovation and Technology Office for Life Sciences D of H and SC, editor. gov.uk; 2023. Available from: https://www.gov.uk/government/publications/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review/commercial-clinical-trials-in-the-uk-the-lord-oshaughnessy-review-final-report#executive-summary

34. Muller A. FDA approves first topical gene therapy. Nat Rev Drug Discov [Internet]. 2023;22(7):527. Available from: https://www.nature.com/articles/d41573-023-00103-y

35. NHS England. NHS England strikes deal on life-saving gene-therapy drug that can help babies with rare genetic disease move and walk [Internet]. 2021. Available from: https://www.england.nhs.uk/2021/03/nhs-england-strikes-deal-on-life-saving-gene-therapy-drug-that-can-help-babies-with-rare-genetic-disease-move-and-walk/

Appendices

Appendix 1

The consent agreement was completed online prior to commencing the survey. This was reiterated at the start of the interview where verbal consent was gained from the participants.

Introduction and purpose

The purpose of the research study is the identification and analysis of clinical trial Gene Therapy Medicinal Products (GTMP) patient referral pathways in the UK and to highlight best practice and enabling transition of referral processes from clinical trial to standard of care. After analysis of GTMP referrals pathways and recommendations for improvements we plan to produce a white paper of our findings. The delivery team consists of the DMD Hub coordination team based at Newcastle University and the Northern Alliance Advanced Therapy Treatment Centre (NA-ATTC).

We will be conducting brief surveys followed by interviews. You are one of approximately 7 sites being asked to participate in the survey and interview. Staff from Newcastle University will collect and analyse the study data.

You are eligible to participate in this study because you work within the NHS and provide clinical care for patients who could potentially be involved in clinical trials with GTMP's and or receive GTMP's as a licensed product, you are at least 18 years old, and you live in the United Kingdom.

Procedures

If you agree to participate, you will first answer a survey on the following pages about your experiences of GTMP patient referral pathways in the UK. The survey will take approximately an hour to complete.

You are able to save the survey and complete at a later date using the **Finish later** option at the bottom of each page. When you click on this, you will be taken to a new page containing a unique URL for your survey. You can either bookmark this URL, or it can be emailed to you. Please note that you must save the link yourself, as we are not able to recover unfinished surveys.

After the survey, Newcastle University staff will contact you to schedule a one-on-one interview. The interviews will be done on Zoom. A researcher from the DMD Hub coordination team based at Newcastle University will conduct the interview. We will ask you questions about your experiences with GTMP referral processes for clinical trials and medical products (such as GTMP) specific to your centre.

Benefits

There is no direct benefit to you for participating. However, your contribution to this project may assist the project team in producing set of recommendations for improved, standardised future practice for (GTMP) patient referral pathways in the UK. The publication will be made freely available and your contribution will be acknowledged appropriately.

Risks

There are no known risks to participating in this study. You do not have to answer any question that you don't want to answer.

Confidentiality

We will take precautions to keep the information you share confidential. We are committed to protecting the rights and privacy of individuals in accordance with the Data Protection Act 2018 and the General Data Protection Regulation. Further information about Data Protection at the University can be found here.

The DMD Hub at Newcastle University will have your full name and your contact information so they can schedule the interview. With your permission, we will record the interviews. Recordings will then be transcribed using a secure file transmission process. The transcripts will be stored on Newcastle University's secure IT network. At the end of the study analysis, we will destroy the electronic recordings. All electronic transcripts of the recordings will be stored in a secure file at Newcastle University for no longer than 5 years after the project ends. We will include summaries and brief quotes in the study findings, but the study team will never disclose your name or contact information and will not assign quotes directly to individuals.

Reimbursement

You will not receive any reimbursement for participating in this study.

Right to refuse or withdraw

Your participation in this study is voluntary. You can choose not to talk about any topic and can withdraw from the interview for any reason at any time without penalty.

Your consent

1. ***Please indicate that you have read and understood this consent form and if you agree to participate in this study.*** *Required*

I have read and understood the information on this page and agree to participate in this study

I no longer wish to participate in this study