Methodology for DMD Care UK: Cardiac Working Group

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1. Background

DMD Care UK is a collaborative initiative between the John Walton Muscular Dystrophy Research Centre (JWMDRC) at Newcastle University and Duchenne UK (DUK), a leading patient charity representing people living with Duchenne muscular dystrophy (DMD) and their families.

The project aims to improve and harmonise care for all people living with DMD across the whole of the UK by developing UK-relevant, practical, evidence and expert opinion-based guidelines for best care in all aspects of DMD. These are accompanied by co-created, patient and family guides to the same care in order that people living with DMD can become informed, active participants in their own care decisions.

Underpinning DMD Care UK is the belief that, no matter where patients live in the UK, they should feel confident that the best care will be provided.

Officially established in 2020 with infrastructure funding from DUK, Duchenne Research Fund (DRF) and Joining Jack (JJ), DMD Care UK has, to date, finalised guidelines in eight areas of care through evidence review, consensus-building and consultation. The project is close to finalisation, or working on, seven additional areas with an expectation that more will be added – including those most relevant to adult care.

1.1 Project Infrastructure

The overall project infrastructure is shown in figure 1.

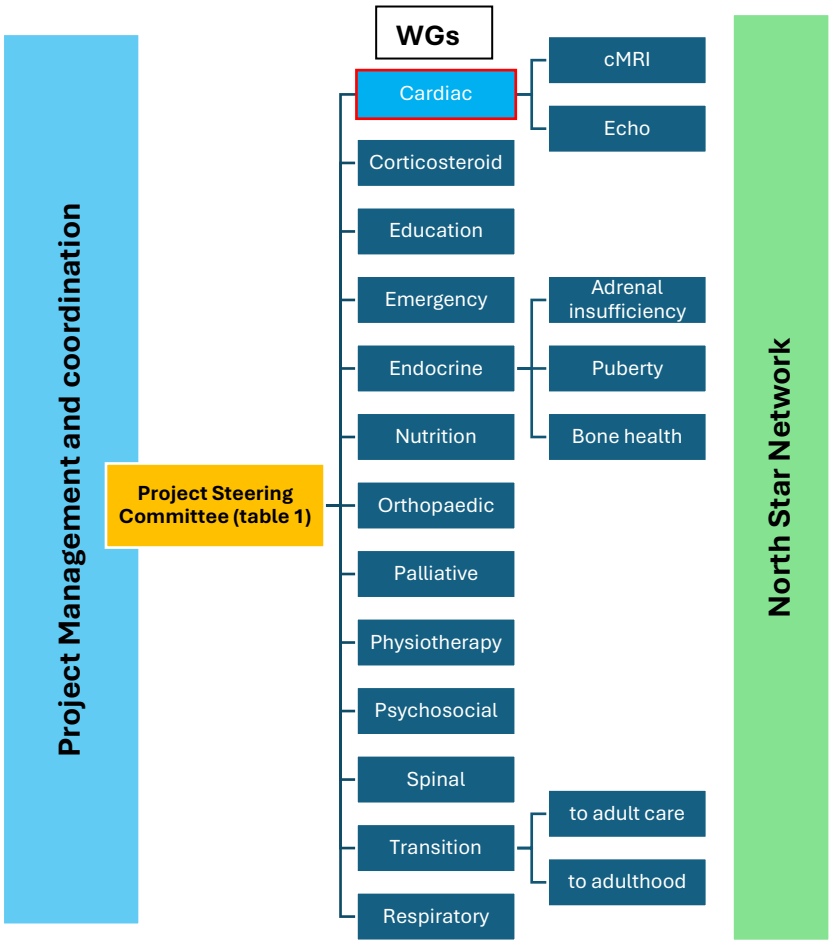

Figure 1: DMD Care UK Project Structure

The **project steering committee (SC)** (table 1) takes a strategic oversight of the project. They input to and sign-off project workplans and take decisions that affect funding and project strategy as well as approving actions that have an impact across the whole project or that deviate from the workplan.

Dedicated and specialist project management is provided and coordinated by funded posts at the JWMDRC, managed by the PI and reporting to the SC.

SC member	**Affiliation**	**Job Role**
Michela Guglieri: ***Project PI and Clinical Lead***	John Walton Muscular Dystrophy Research Centre, Newcastle	Professor of Neuromuscular Disorders
Alex Johnson: ***Patient lead***	Duchenne UK	Co-founder of DUK; Founder of JJ
Cathy Turner: **Project Manager**	John Walton Muscular Dystrophy Research Centre, Newcastle	Senior Project Manager (project-funded)
Giovanni Baranello	Great Ormond Street Hospital London	Consultant Paediatric Neurologist
Anne-Marie Childs	Leeds Teaching Hospitals NHS Trust	Consultant Paediatric Neurologist
Adnan Manzur	Great Ormond Street Hospital London	Consultant Paediatric Neurologist
Ros Quinlivan	National Hospital for Neurology and Neurosurgery London	Consultant in Neuromuscular Diseases
Sheli Rodney	Duchenne Research Fund	Director of Operations at DRF
Anna Sarkozy	Great Ormond Street Hospital London	Consultant Paediatric Neurologist
Tracey Willis	Robert Jones & Agnes Hunt Orthopaedic Hospital Oswestry	Consultant Paediatric Neurologist
Jarod Wong	Royal Hospital for Children, Glasgow	Consultant Paediatric Endocrinologist

Table 1: DMD Care UK Project Steering Committee

Each of the WGs follows a similar methodology outlined in section 2.1 below. Specific details for how that methodology was implemented, for the creation of cardiac care guidelines are given in section 2.2.

1.2 Project Funding

DMD Care UK is funded by grants from patient organisations to support the project management and coordination. Funded posts for this are based at Newcastle University. As a rule, WG or other SC members receive no funding for time or input to guidelines and their participation is entirely voluntary. Where patient organisations have also funded specific WG-based roles, this is detailed in that WG section. None of the WGs receives any funding from industry.

2. Project Methodology

2.1 outline model for all WGs

A two-day North Star (NS) meeting in May 2019 was organised to discuss standards of care (SoC) for DMD and the need for a national initiative to improve implementation. In advance of the meeting, a questionnaire-survey based on International 2018 SoC[1-3] was circulated to all paediatric North Star Centres (Appendix A) with results collated to present to attendees. This served several purposes:

- Illustrated the need for a SoC project in the UK including to the people who needed to engage with the process
- Identified where gaps in implementation were due to:
    - Lack of awareness of recommendations
    - Lack of evidence or consensus (and so 'belief' in the recommendation)
    - Lack of resource/feasibility
- Supported decision making about priority areas for first WGs

The first WGs were selected in areas where the survey suggested that implementation would be increased through awareness-raising and consensus-building rather than where there were significant problems with resources.

As a result, an early 'pilot' working group was established for Bone and Endocrine Care to test the project concept. This is an area that affects most people with DMD from an early age because of the widespread use of corticosteroids. In addition, awareness and consensus on endocrine management were seen as the main barriers to harmonised best care, rather than financial resource needs.

Subsequent WGs were then identified to mirror those areas of care outlined in the International Standards[1-3] and prioritised by the SC informed by the survey as detailed above. Alongside the pilot group for Bone and Endocrine, the SC agreed to start groups for Cardiac Care and Respiratory Care. Again, gaps in care in these areas were seen as *primarily* due to lack of evidence/consensus and lack of awareness of the best SoC.

The steps agreed for each WG were as follows:

Recruitment of experts: WG leads are suggested by members of the SC, based on experience and expertise in their field and in DMD and on their research activity, and invited by the project management team.

In discussion with the agreed WG lead and SC, core members are invited to join from adult and paediatric backgrounds, based on their profile, expertise and geographical spread.

An invitation is then sent to the paediatric NS neuromuscular network to a) provide a list of the relevant specialists at their centre – this is the basis of our consultation network; b) suggest which of those to approach for additional, full WG membership.

Volunteers from the patient community are invited to join WGs that align with their areas of interest – these are identified through project contacts, Duchenne UK, Joining Jack, Duchenne Research Fund.

The WG provides additional contacts for any perceived 'gaps' in expertise (e.g. in adult care).

The aim is to achieve multi-disciplinary WGs with neuromuscular (DMD) experts, sub-specialty experts (e.g. cardiologists or orthopaedic surgeons with experience in DMD), others as needed (e.g. endocrinologists for the corticosteroid WG) and patient/carer-representatives.

WG membership is generally kept to maximum of 15 members to allow productive, focused discussion on the relevant topic. Where there are more potential members, a selection is made based on different areas of experience (e.g. adult and paediatric; community and specialist centre) and on geography.

Each WG undertakes to follow the process below. Specific detail for the cardiac care WG is given in section 2.1:

a. Review international SoC guidelines published in 2018 [1-3], and relevant literature.

b. Review current practice in the UK, using WG experience and building on the survey undertaken in 2019 (Appendix A).

b. Identify the relevant professional body and connect with them to establish their process for endorsement.

c. Draft UK-relevant, practical guidelines, based on the international standards, additional evidence, expert experience and opinion and the practicalities of the NHS set-up. Pay particular attention to gaps in provision or significant barriers identified in current practice. This is done through a series of online meetings over a period of 6 months or more.

d. Once a first draft is agreed by the WG, send for feedback on completeness, acceptability, practicality, validity to:

    - specialists in that WG field (the consultation network) identified at set up
    - the wider NS network neuromuscular leads
    - professional bodies as needed/agreed with them at set-up
    - other key expert groups as required, including other WGs, e.g. the endocrine WG for review of the orthopaedic and corticosteroid guidelines

e. Discuss feedback received with the whole WG and make agreed changes

f. Recirculate the document (as version 2) for final broad consensus agreement *or* additional comment, depending on level of divergence of opinions

g. Continue this process until consensus reached (2-5 cycles is expected)

h. Finalise guideline, confirm endorsement, seek publication as a paper in appropriate peer reviewed, open access journal if appropriate

i. Patient representatives, with support from the project management team, draft a family guide which is reviewed by clinicians in the WG for correctness and by a wider family focus group for appropriateness and accessibility

j. Paper published and family guide released at the same time where possible

k. Dissemination via DMD Care UK website, local and national networks, local, national and international meetings. Since 2025, via a healthcare professional education programme within DMD Care UK (DECRI):

https://decri-nmdtraining.talentlms.com/plus/

l. WG continues to meet to discuss education and dissemination, missing evidence and research questions to be addressed, requirements for update of the guideline based on availability of new evidence

m. Updating of the guideline via the WG happens **no later than every 3 years** (sooner if there are new developments or significant new evidence in the field)

2.2 Cardiac Guideline Development

2.2.1 Scope and Purpose:

The DMD Care UK cardiac WG was launched in November 2020. The cardiac care guideline was published in BMJ Open Heart, October 2022[4].

This aims to promote a uniform high standard of cardiac care across the UK for children with dystrophinopathy as well as establishing recommendations on the cardiac care of females at risk of cardiomyopathy because they carry mutations in the *DMD*-gene. It is also of relevance for those treating the related Becker muscular dystrophy (BMD) caused by in-frame mutations in the DMD gene.

It targets neuromuscular specialists and, importantly, cardiologists involved in the care of people with DMD, even (and especially) where they are not experts in the condition.

The key health questions covered by this guideline are:

- How to best preserve cardiac function from the beginning in people with DMD
    - How should cardiac medications be initiated and titrated in people with DMD?
    - Does non-invasive nocturnal ventilation have an impact on cardiac function in DMD
    - Is there a role for implantable devices for cardiac management in DMD?
    - What is the impact of long-term steroid treatment on the heart in DMD?
- How to identify dystrophinopathy, monitor and preserve heart-function in carrier females

and were included in the evidence review (see section 2.2.3 and Appendix B)

2.2.2 Stakeholder Involvement

The Cardiac WG was launched in November 2020 comprising the **16 members listed in Table 2**.

The group broadly followed the process outlined in 2.1 above and specific detail for how stakeholders were included in the cardiac guideline development is included below. Clinical stakeholders were identified through the pre-existing **North Star (NS) Network** of specialist neuromuscular centres.

Name	**Expertise**	**Affiliation**
John Bourke, Clinical Lead	Consultant Cardiologist and Electrophysiologist	Freeman Hospital, Newcastle
Lisa Kuhwald, Patient Lead	Patient Expert	Independent
Dr Kadhim Kadhim, incoming Clinical Lead	Consultant Cardiologist and Electrophysiologist	Freeman Hospital, Newcastle
Alex Johnson	Patient Expert	Duchenne UK
Ros Quinlivan	Consultant in Neuromuscular Diseases	National Hospital for Neurology and Neurosurgery London
Caroline Coats	Consultant Cardiologist	University of Glasgow
Michela Guglieri (PI)	Professor of Neuromuscular Disorders	Newcastle University
Zaheer Yousef	Consultant Cardiologist	Cardiff and Vale University Health Board - Cardiothoracic Services
Adrian Morley-Davies	Consultant Cardiologist	The Robert Jones and Agnes Hunt Orthopaedic Hospital
Maria Ilina	Consultant Cardiologist	Scottish Paediatric Cardiac Service
Stam Kapetenakis	Consultant Cardiologist	Lane Fox (London) joint cardiorespiratory neuromuscular programme
William Bradlow	Consultant Cardiologist	University Hospitals Birmingham
Ashish Chikermane	Consultant Cardiologist	Birmingham's Women's and Children's Hospital

Matthew Fenton	Consultant Cardiologist	Great Ormond Street Hospital London
Konstantinos Savvatis	Consultant Cardiologist	Barts Heart Centre London
Marianela Schiava	Clinical Research Associate in Neuromuscular Diseases	John Walton Muscular Dystrophy Research Centre, Newcastle

Table 2: Cardiac WG members

Every child with DMD in the UK should be seen at one of these 24 centres for routine clinical appointments. For adults, the NS network is newer and less established, however, we were able to reach out to a number of adult specialists via the adult network. In this way, our cardiac WG was able to reach the vast majority of neuromuscular consultants responsible for DMD care, and the key cardiologists in their team. This resulted in identification of a total of 106 clinical experts (59 neuromuscular leads and 47 cardiologist experts involved in care of people with DMD). All were contacted as part of the external review process.

In addition, we engaged with the British Cardiovascular Society (BCS) in the development and endorsement of the guideline and have presented the outputs at their annual conference (https://heart.bmj.com/content/109/Suppl_3/A8).

Two representatives from the patient community were part of the WG and received the same materials, joined discussions and signed off on versions in the same way as the clinician members. They are authors on the published guideline paper.

Family guide

A wider group of patients and family members were consulted on the development of a family guide after finalisation of the clinical guideline. This can be seen here: https://res.cloudinary.com/studio-republic/images/v1667319865/DMD-Care-UK-Cardiac-patient-information-digital/DMD-Care-UK-Cardiac-patient-information-digital.pdf?_i=AA

The purpose of this was to make the care recommendations clear to patients and families and to explain evidence and rationale behind them. This serves to empower patients and enables those who want to, to highlight care standards to their medical teams which helps to increase implementation and awareness.

The first draft of this family guide was written by the cardiac WG patient experts and project coordination team and shared with DMD Care UK's family focus group made up of 25 members (4 adults living with DMD and 22 parents or carers). Comments on the text were invited by email and meetings convened to run through these as a group, agreeing on changes needed. This included:

- Changing terminology
- Adding statements to make the recommendations and rationale clearer
- Adding sections that were felt to be important but missing

A revised version was circulated to the same group and a second round of edits incorporated in the same way. This was developed by a design team and a final version was sent to the cardiac care WG and the family focus group for sign off.

2.2.3 Rigour of Development

Clinical and disease context

DMD is a rare disease – in the UK there are around 2500 people living with the condition (https://www.nice.org.uk/guidance/gid-ta10310/documents/draft-scope-pre-referral#:~:text=The%20incidence%20rate%20of%20Duchenne,the%20major%20aims%20of%20treatment.) When developing a clinical guideline for standards of care this has an advantage in that expertise is concentrated in an established network of specialist centres (the North Star network) and it has therefore been possible to send a draft for review to the vast majority. However, DMD's rarity brings the disadvantage that research is limited and there is far less high-level evidence (from RCTs for example) across different aspects of care.

For cardiac care in particular, intervention that is recommended early in the disease course is expected to have impact much later – slowing the development of cardiomyopathy for example. The outcomes of this early intervention may not be *clinically* meaningful until as much as 10 or more years later. This precludes collecting evidence from placebo-controlled RCTs and measuring benefit therefore relies on long-term systematic data collection across care centres.

Meanwhile, interpretation of any benefits of early cardio-protective measures needs to be conducted against a complex clinical care package over many years with different corticosteroids and other concomitant medications, different mutations, lifestyle factors and other variables.

For these reasons, the DMD Care UK Cardiac Guideline relies on expert opinion, assumptions based on understanding of the disease mechanisms, and clinician and patient experience as well as more robust data where it exists.

Methods used for evidence search

Dr Marianela Schiava (Newcastle) undertook a literature search, the full details of which, including search strings and results are given in Appendix B.

A series of key areas or questions were identified and distinct searches with specific foci in each undertaken using PubMed (Table 3). Some articles were intentionally selected for inclusion based on established relevance to the topic

Cardiac Management in Duchenne Muscular Dystrophy Summary
Cardiac Involvement in Carriers of Duchenne and Becker Muscular Dystrophies based on Echocardiogram, Electrocardiogram and Biomarkers findings
Cardiac MRI and Cardiac Involvement in Carriers of Duchenne/Becker Muscular Dystrophy

Table 3: Three main search areas used for literature search

Criteria used for evidence selection

Filters were applied to search results to identify evidence to be included. These were based on the following list and full details are given in Appendix B:

- **Publication date**
- **Text availability**
- **Article attribute**
- **Article Type**
- **Article Language**
- **Species**
- **Sex**
- **Age**

Clear inclusion and exclusion criteria were set and full details of these are in Appendix B:

Strength and limitations of the body of evidence

The literature search conducted by Dr M. Schiava was presented to the cardiac WG in February 2021. It identified the level of evidence for each item included, from 1(RCT) to 5 (expert opinion). This evidence level was not included in detail in the published guideline due to word count restrictions. However, where robust evidence is particularly lacking (on the early prophylactic use of heart-slowing medications for example) this is acknowledged in the publication, and the clinical context and justification for its inclusion is given.

Formulation of guideline

Informed by the evidence review, key elements of cardiac care requirements for people with DMD were identified and discussed at a series of WG meetings until broad consensus was reached on each. These were guided by an agreed principle within the group that:

- we should recommend making sensible, expert decisions rather than relying on clinical evidence for heart involvement (because this is often too late)
- care for the heart in DMD should be proactive rather than reactive

An outline v1 was drafted by the WG's clinical lead (Dr John Bourke) for WG-review with comments returned to the project management team on individual word documents rather than using a shared document. This was to prevent influence and bias within the group.

These comments were then discussed at an online WG meeting, steps towards consensus made by discussion, revisions incorporated and the process repeated over four online meetings between January and September 2021 to discuss feedback and agree revisions. Formal voting processes were not used, but open discussion combined with a continued in-advance opportunity to give input on word documents were used to reach broad agreement.

By September 2021, the WG were unanimous in finalising the guideline (v10) for wider external review (see *External review process* below).

Considerations of benefits and risks

The published paper gives guidance on benefit/risk considerations of elements of the care recommendations, including clear pathways to be followed to mitigate risks where different treatment choices are possible. These can be seen in Figures 1 and 2 of the published guideline.

Specific consideration is given to where risks of cardiac MR imaging may outweigh the benefits to clinical management, identifying some groups of patients in which it would be contraindicated. In addition, the risks of gadolinium exposure are highlighted and mitigation of these is included.

How the recommendations are linked to evidence

Throughout the guideline, the recommendations are fully referenced based on the evidence identified by the literature review. During the external review process, where additional evidence was highlighted, this was considered by the WG and included where it also met the inclusion criteria. This was particularly important for evidence published after the time of the literature review.

External review process

v10 of the guideline, approved by the WG was circulated by email to the cardiologists identified by paediatric NS centres and adult neuromuscular specialists as managing cardiac care for DMD patients as described in 2.2.2 above. Feedback was requested via the form shown in figure 2 within 28 days (reminder sent at 21 days).

Cardiac management of Duchenne muscular dystrophy

Below are the draft guidelines from the DMD Care UK Cardiac working group Please provide comments or queries here and email to catherine.turner@ncl.ac.uk by 30th September. Thank you.

Comments from: xxxxxxxx

Figure 2: feedback form for input from cardiology specialists in September 2021

Feedback received was collated, shared with the WG, then discussed and consensus reached on revisions needed considering this feedback. An updated version was agreed (v12) and submitted to the British Cardiovascular Society for review on 29 October 2021. Feedback was received and after further discussion and revisions, resulted in a v16 considering feedback from BCS and agreed by the WG. This was submitted to BCS for endorsement on 3 December 2021 and shared for final review by neuromuscular specialists across the NS networks on 10 December 2021.

Endorsement was received from BCS on 17th December 2021:

'*We have gone through our (new) internal process for endorsement of such documents. I'm glad to say the BCS would be pleased to endorse your document and our committee felt there was a lot of value in the document that we would support.'*

Final comments received from the NS review and formatting suggestions from BCS were discussed at a sign-off meeting with the WG and DMD Care UK project Steering Committee which resulted in an eventual v18 which was published in BMJ Open Heart in October 2022 (submitted February 2022, revised and accepted September 2022).

2.2.4: Clarity of presentation

The guideline has been presented via an open access, peer reviewed cardiac journal. It summarises recommendations using clear algorithms with references and alternative actions as needed in Figures 1 and 2 of the publication.

The key recommendations are highlighted in the published paper targeting clinicians, and in the guide for patients and families in order that can know what good care looks like and can support awareness raising and wider implementation.

2.2.5: Applicability

Full cost/resource analysis of implementing the guideline has not been undertaken. However, *lack of access* to cMRI was identified as a barrier to this modality of imaging in the 2019 clinician survey (Appendix A). Meanwhile, patients/families reported low numbers of cMRIs in a 2021 survey coordinated by DMD Care UK (figure 3) with 82% never having had one. Whilst this needs to improve to deliver the care described by Bourke et al[4], the authors of the guideline recognised that it was unrealistic to expect a rapid increase in the number of scanners available. Against this reality, the additional importance of prophylactic use of cardio-protective medication was further highlighted. This message was repeated to the patient community in the Cardiac Care Family Guide to reduce the anxiety people were anecdotally reporting about their/their sons' need for cMR imaging (figure 4).

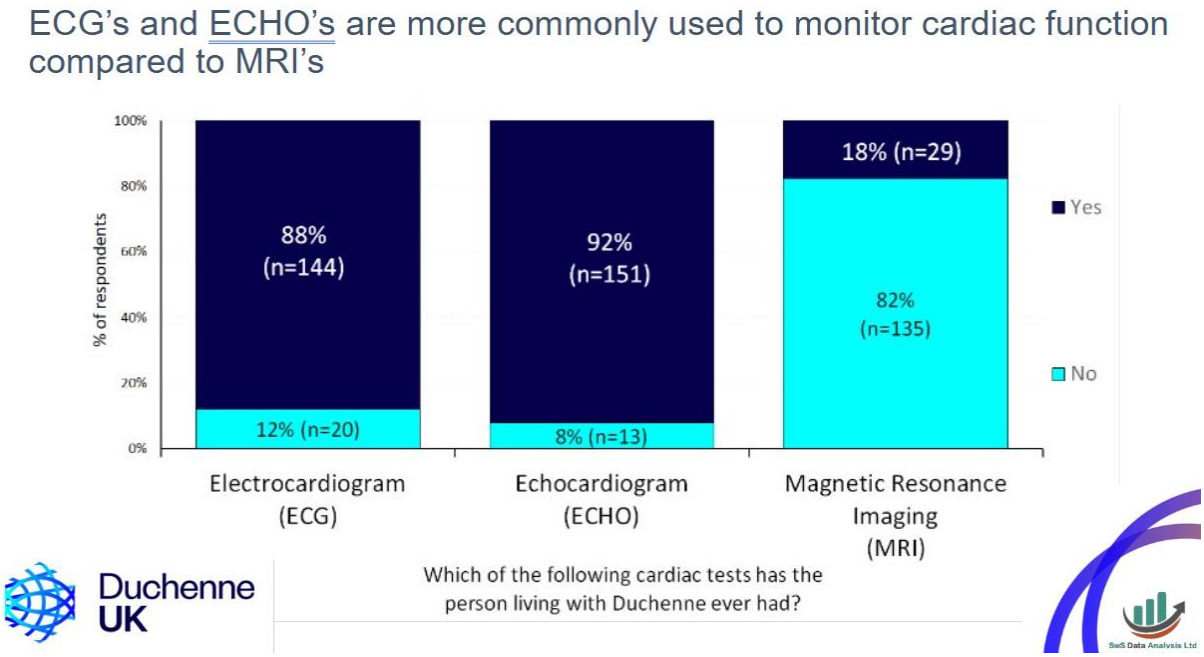

Figure 3: Screenshot from results of a patient-community survey in 2021 on SoC (164 respondents).

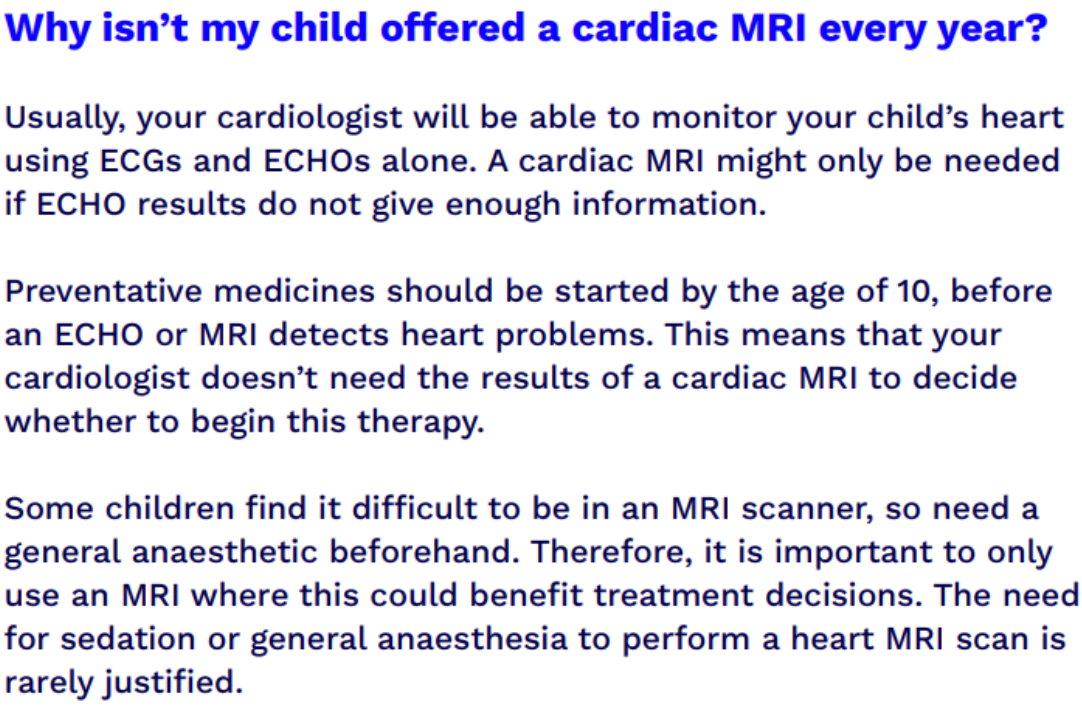

Figure 4: screenshot from Cardiac Care Family Guide (https://www.duchenneuk.org/wp-content/uploads/2022/11/DMD-Care-UK-Cardiac-patient-information-digital.pdf)

Importantly, the cardiac care guideline for clinicians[4] aims to facilitate implementation of the recommendations by providing practical recommendations. Based on these, a proposed audit is provided to support centres in evaluating their own delivery and then engage in service quality improvement. This can be seen in Box 1 of the publication[4].

As DMD Care UK, we are now measuring implementation across the UK in order that we can track progress, measure impact on patient care, and identify remaining barriers. To do this, two years after open access publication, an audit was conducted of paediatric and adult NS sites against the key points from the guideline. Centres were asked to respond to questions about specific aspects of cardiac care delivery based on 20 consecutive patients. The data from this is currently in analysis and will be presented via a poster at World Muscle Society in October 2025.

2.2.6: Editorial Independence

This guideline was developed by an independent WG of voluntary experts who received no funding for their participation.

The infrastructure of the overall DMD Care UK project (figure 1 above) receives some salary funding and travel budget for project management at Newcastle University. The salary of WG lead (Dr John Bourke) is funded for 0.5 days per week at the NHS Trust. All this funding comes exclusively from three patient organisations as described supported by charitable donations. No funding is received from industry for this work.

In addition, publication of the guideline in BMJ's Open Heart required a declaration of conflict of interest for all the participants (authors) and there were none. Funding from the patient organisations was for infrastructure only and not for the work or members of this cardiac WG.

This methodology document should be read alongside:

Cardiac care of children with dystrophinopathy and females carrying DMD-gene variations[4] : https://doi.org/10.1136/openhrt-2022-001977

Information for patients and families Cardiac care for Duchenne muscular dystrophy: https://www.duchenneuk.org/wp-content/uploads/2022/11/DMD-Care-UK-Cardiac-patient-information-digital.pdf

References

1. Birnkrant DJ, et al; Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol. 2018 Mar;17(3):251-267. doi: 10.1016/S1474-4422(18)30024-3.

2. Birnkrant DJ, et al; Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. Lancet Neurol. 2018 Apr;17(4):347-361. doi: 10.1016/S1474-4422(18)30025-5.

3. Birnkrant DJ, 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 May;17(5):445-455. doi: 10.1016/S1474-4422(18)30026-7

4. Bourke J, et al., Cardiac care of children with dystrophinopathy and females carrying DMD-gene variations, Open Heart 2022;9:e001977. doi: 10.1136/openhrt-2022-001977

Appendix A: Questions used to survey NS centres on implementation of international SoC in 2019.

If any of the areas below are not fully implemented, please comment on the reasons (eg because of lack of resource or because of lack of evidence for the benefit)

1. Respiratory Care

At what age do you start to perform spirometry?

How often do you perform spirometry in ambulant patients?

How often do you perform spirometry in non-ambulant patients?

Do you measure peak cough flow?

Do you measure MIP and MEP?

Can you provide pulse oximetry for home recording of SpO2?

Provision of Lung Volume Recruitment Bag when FVC <= 60% predicted?

Prescription of mechanically assisted coughing when FVC <50% predicted, PCF <270 L/min, or MEP <60 cm H2O

Initiation of nocturnal non-invasive ventilation when there are signs and symptoms of sleep hypoventilation?

Initiation of nocturnal non-invasive ventilation when FVC is less than 50% predicted, MIP <60 cm H2O, or awake baseline SpO2 <95% or pCO2 >45 mm Hg?

Initiation of nocturnal non-invasive ventilation when sleep study shows petCO2 or ptcCO2 > 50 mm Hg for at least 2% of sleep time, or SpO2 of 88% or less for at least 2% of sleep time or an apnoea–hypopnoea index of five events per hour or more?

2. Cardiac Care

At what age do your patients most commonly have their first / baseline cardiac checks?

12-lead ECG/Echocardiogram/Cardiac magnetic resonance imaging/Other

For age <10 years old: How frequently do you repeat cardiac testing if ventricular function was normal previously?

For age = or >10 years old: How frequently do you repeat cardiac testing if ventricular function was normal previously?

Initiation of the following: ACE-inhibitor/ ARB/ Sacubitril-Valsartan/ Beta-blocker/ Mineralocorticoid receptor blocker/ Other is based on:

- Prophylactic initiation (based on age alone) with normal LV-function
- Prophylactic initiation routinely based mainly on cardiac MRI parameters
- ECHO Imaging showing left ventricular dysfunction (EF%, FS%, etc)
- Detection of Fibrosis on Cardiac MRI

- Other

How often do you arrange cardiac monitoring for female carriers?

Routinely perform a cardiac MRI in subjects aged > 6-7 years

Can you perform cardiac MRI at your centre?

If yes, when do you refer for a cardiac MRI?

Advise implantable cardioverter defibrillators for individuals with an ejection fraction < 35%?

3. Psychosocial Health

Do you ask patients about their mental health?

Informally in clinic/ Formally in clinic (questionnaire)/ Formally in clinic (by adequately trained personnel)/ No

Do you use?

Strengths and Difficulties Questionnaire/ PARSIII/ Patient Health Questionnaire 9-item depression scale/ Generalized Anxiety Disorder 7-item scale/ None/ Other

Does your team have a mental health professional (ie, psychologist or psychiatrist) with training and experience in assessing and treating psychiatric conditions in the context of chronic medical or neurodevelopmental conditions

4. Bone and endocrine

When do you perform lateral spine X-imaging to detect vertebral fractures in steroid treated boys?

Are patients with DMD routinely prescribed vitamin D supplementation?

Do you recommend bisphosphonate IV therapy for boys with DMD on steroids?

Do you examine puberty in the neuromuscular clinic?

Please state the age at which you undertake this examination

Do you routinely prescribe testosterone for pubertal induction?

What is the youngest that you prescribe testosterone for pubertal induction for boys with DMD?

Do you discuss adrenal suppression and the risk of adrenal crisis with DMD boys on steroids?

Do you provide your DMD boys on steroids injectable hydrocortisone for use at home in severe illness?

Do you educate families to inject hydrocortisone at home during severe illness?

Do you perform lateral spine X-ray every 1-2 years in all subjects on steroids?

For each of the endocrine and bone SOC, please state whether at your centre these are fully implemented, partially implemented or not implemented:

- Perform lateral spine X-Ray every 2-3 years in subjects not on steroids

- Perform DEXA scan for spine bone mineral density annually –
- Measure serum 25-hydroxyvitamin D3 annually in all DMD subjects
- Perform physical assessment of pubertal status by Tanner staging every 6 months starting by age 9 years

Appendix B: Search Strategy

Search Strategy Documentation: Cardiac Management in Duchenne Muscular Dystrophy Summary

Date of Search: January 1-31, 2021.

Database Used: PubMed (https://pubmed.ncbi.nlm.nih.gov/)

Search Keywords & Medical Subject Headings (MeSH) – Please note that the terms listed below were combined in various ways during the search process. As a result, some references may appear more than once across different search iterations, potentially leading to duplication within the reference list.

("Duchenne muscular dystrophy" OR "DMD")

AND ("cardiomyopathy" OR "heart failure" OR "cardiac function")

AND ("management" OR "treatment" OR "intervention")

Search String 2 (Narrower, focused on pharmacological treatment or interventions)

("Duchenne muscular dystrophy")

AND ("angiotensin-converting enzyme inhibitors" OR "beta-blockers" OR "corticosteroids" OR "idebenone" OR “eplerenone” OR "defibrillators")

AND ("cardiomyopathy" OR "cardiac dysfunction")

("Duchenne Muscular Dystrophy") AND ("Cardiomyopathy") AND ("Defibrillators")

Search String 3 (Focused on guidelines and consensus papers)

("Duchenne muscular dystrophy" OR “DMD")

AND ("cardiac" OR "cardiomyopathy")

AND ("guideline" OR "consensus")

Filters Applied on Pubmed

- **Publication date:** Custom Range 01/01/1999 – 29/01/2021(1999 was used as the prescription of glucocorticoid was more homogeneous since that late 1999).
- **Text availability:** Abstract, Free full text, Full text
- **Article attribute**: none
- **Article Type:** Clinical Trial, Consensus Development Conference, Guideline, Meta-Analysis, Multicenter Study, Observational Study, Practice Guideline, Randomized Controlled Trial, Systematic Review.

- **Article Language:** English
- **Species:** Humans
- **Sex:** Male
- **Age:** no age limit applied
- **Other:** none

Inclusion Criteria

- Peer-reviewed articles
- Studies addressing cardiac surveillance, pharmacologic cardiac treatments with and without glucocorticoid treatment, interventional cardiac treatments
- Guidelines and systematic reviews
- Studies involving human subjects with DMD with no age limit

Exclusion Criteria

- Non-English publications
- Animal studies
- Case reports without broader relevance

Comments

- Please note that the articles included in the Cochrane review (Bourke JP, Bueser T, Quinlivan R. Interventions for preventing and treating cardiac complications in Duchenne and Becker muscular dystrophy and X-linked dilated cardiomyopathy. Cochrane Database Syst Rev. 2018 Oct 16;10(10):CD009068. doi: 10.1002/14651858.CD009068.pub3. PMID: 30326162; PMCID: PMC6517009.) were then read and analysed separately and included in the review.

- Certain articles were intentionally selected for inclusion in the review based on their established relevance to the topic, including:

- Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol. 2010;9(2):177-189. doi:10.1016/S1474-4422(09)70272-8

- Bourke JP, Guglieri M, Duboc D, et al. 238th ENMC International Workshop: Updating management recommendations of cardiac dystrophinopathyHoofddorp, The Netherlands, 30 November - 2 December 2018. Neuromuscul Disord. 2019;29(8):634-643. doi:10.1016/j.nmd.2019.06.598

- Jessup M, Bozkurt B, Butler J, et al. ACCF / AHA Practice Guideline 2013 ACCF / AHA Guideline for the Management of Heart Failure A Report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines. 2013:240-327. doi:10.1161/CIR.0b013e31829e8776

- Eagle M, Baudouin S V., Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: Improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002;12(10):926-929. doi:10.1016/S0960-8966(02)00140-2

- Cripe LH, Tobias JD. Cardiac considerations in the operative management of the patient with Duchenne or Becker muscular dystrophy. 2013;(9):777-784. doi:10.1111/pan.12229

Search Strategy Documentation: Cardiac Involvement in Carriers of Duchenne and Becker Muscular Dystrophies based on Echocardiogram, Electrocardiogram and Biomarkers findings.

Date of Search: January 1–31, 2021
Database Used: PubMed (https://pubmed.ncbi.nlm.nih.gov/)

Search Keywords & Strategy

Please note that the terms listed below were combined in various ways during the search process. As a result, some references may appear more than once across different search iterations, potentially leading to duplication within the reference list

Search String 1 – Broad Search (General Cardiac Involvement in Carriers)

("Duchenne muscular dystrophy" OR "Becker muscular dystrophy")

AND (carrier OR carriers OR heterozygote)

AND ("cardiac involvement" OR "cardiomyopathy" OR "heart function" OR "troponin" OR "BNP" OR "echocardiography")

Search String 2 – Imaging and Diagnostics Focus

("Duchenne muscular dystrophy" OR "Becker muscular dystrophy")

AND (carrier OR carriers)

AND ("cardiac MRI" OR "echocardiography" OR "troponin" OR "brain natriuretic peptide" OR "BNP")

Search String 3 – Focused on Management and Monitoring

("Duchenne muscular dystrophy" OR "Becker muscular dystrophy")

AND (carrier OR carriers)

AND ("cardiac surveillance" OR "cardiomyopathy management" OR "cardiac monitoring")

Filters Applied in PubMed

- **Publication date:** Custom range from 01/01/1999 to 29/01/2021
- **Text availability:** Abstract, Free full text, Full text
- **Article type:** Clinical Trial, Guideline, Observational Study, Practice Guideline, Systematic Review
- **Language:** English
- **Species:** Humans
- **Sex:** Female
- **Age:** No restriction

Inclusion Criteria

- Peer-reviewed articles

- Studies addressing **cardiac surveillance, diagnosis, monitoring, or treatment** of cardiomyopathy in **female carriers** of Duchenne or Becker muscular dystrophy
- Studies involving **human female subjects** identified as **carriers** (no age restriction)
- Systematic reviews, observational studies, or clinical trials

Exclusion Criteria

- Non-English publications
- Animal studies
- Case reports without generalizable insights
- Studies focused solely on **affected male patients** with DMD or BMD

Search Strategy Documentation: Cardiac MRI and Cardiac Involvement in Carriers of Duchenne/Becker Muscular Dystrophy

Date of Search: January 1–31, 2021
Database Used: PubMed (https://pubmed.ncbi.nlm.nih.gov/)

Search Keywords & Strategy

Please note that the terms listed below were combined in various ways during the search process. As a result, some references may appear more than once across different search iterations, potentially leading to duplication within the reference list

Search String 1 – Cardiac MRI in Carriers

("Duchenne muscular dystrophy" OR "Becker muscular dystrophy")

AND (carrier OR carriers)

AND ("cardiac magnetic resonance" OR "cardiac MRI" OR "CMR")

Search String 2 – Myocardial Fibrosis, LGE, and Function in Carriers

("Duchenne muscular dystrophy" OR "Becker muscular dystrophy")

AND (carrier OR carriers)

AND ("myocardial fibrosis" OR "late gadolinium enhancement" OR "LGE" OR "ventricular dysfunction")

Search String 3 – Comparative Imaging Studies (Carriers vs Affected Males)

("Duchenne muscular dystrophy" OR "Becker muscular dystrophy")

AND (carrier OR carriers)

AND ("cardiac MRI" OR "CMR")

AND ("male relatives" OR "comparison" OR "first-degree relatives")

Filters Applied in PubMed

- **Publication date:** Custom range from 01/01/1999 to 29/01/2021
- **Text availability:** Abstract, Free full text, Full text
- **Article type:** Observational Study, Clinical Trial, Comparative Study, Systematic Review
- **Language:** English
- **Species:** Humans
- **Sex:** Female
- **Age:** No restriction

Inclusion Criteria

- Peer-reviewed articles

- Studies utilizing **cardiac magnetic resonance imaging (CMR)** to assess **cardiac structure and function** in **female carriers** of DMD/BMD
- Articles investigating myocardial fibrosis, left ventricular dysfunction, or LGE patterns
- Comparative studies with male DMD/BMD patients included

Exclusion Criteria

- Non-English publications
- Animal studies
- Case reports without broader relevance
- Studies focused solely on male DMD/BMD patients or on skeletal muscle imaging