

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## PRODUCING A PREFERENCE-BASED QUALITY OF LIFE MEASURE FOR PEOPLE WITH DUCHENNE MUSCULAR DYSTROPHY: A MIXED-METHODS STUDY PROTOCOL

|                               |  |
|-------------------------------|--|
| Journal:                      | <i>BMJ Open</i>  |
| Manuscript ID                 | bmjopen-2018-023685  |
| Article Type:                 | Protocol   |
| Date Submitted by the Author: | 18-Apr-2018  |
| Complete List of Authors:     | Powell, Philip; University of Sheffield, School of Health and Related Research; University of Sheffield, Economics<br>Carlton, Jill; University of Sheffield, School of Health and Related Research<br>Rowen, Donna; University of Sheffield, School of Health and Related Research<br>Brazier, John; University of Sheffield, School of Health and Related Research |
| Keywords:                     | Duchenne muscular dystrophy, Patient reported outcome measures, Psychometrics, QUALITATIVE RESEARCH, Quality of life   |
|                               |  |

SCHOLARONE™  
Manuscripts

Peer Review Only

1  
2  
3  
4  
5  
6  
7 **PRODUCING A PREFERENCE-BASED QUALITY OF LIFE MEASURE FOR**  
8 **PEOPLE WITH DUCHENNE MUSCULAR DYSTROPHY: A MIXED-METHODS**  
9 **STUDY PROTOCOL**  
10  
11  
12  
13  
14  
15

16 Philip A Powell,<sup>1,2\*</sup> Jill Carlton,<sup>1</sup> Donna Rowen,<sup>1</sup> John E Brazier<sup>1</sup>  
17  
18  
19

- 20 1. Health Economics and Decision Science, School of Health and Related Research,  
21 University of Sheffield, Sheffield, UK  
22  
23 2. Institute for Economic Analysis of Decision-making, Department of Economics,  
24 University of Sheffield, Sheffield, UK  
25  
26  
27  
28  
29

30  
31 \* Correspondence to Philip A Powell, Health Economics and Decision Science, School of  
32 Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street,  
33 Sheffield, UK, S1 4DA. Email: p.a.powell@sheffield.ac.uk. Tel: + 44 (0) 114 222 0794.  
34  
35  
36  
37  
38

39 Word count (excluding title page, abstract, summary, references, figures and tables): 4515  
40  
41  
42

43 Keywords: Duchenne Muscular Dystrophy; Patient Reported Outcome Measures;  
44 Psychometrics; Qualitative Research; Quality of Life  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

### Introduction

Preference-based measures (PBMs) of health-related quality of life (HRQoL) are used to generate quality-adjusted life years, which are necessary for cost effectiveness evaluations of health interventions via cost utility analysis. These measures of health can be generic (i.e. pan-diagnostic) or condition-specific. No condition-specific PBM of HRQoL in Duchenne muscular dystrophy (DMD) exists, yet there are concerns that standard generic measures lack the specificity to assess aspects of HRQoL that are especially important to people with DMD. This study has been designed to produce a condition-specific PBM of HRQoL in DMD.

### Methods and analysis

This mixed-methods study proceeds through three stages. In the first stage (concept elicitation), semi-structured interviews will be conducted with boys and men diagnosed with DMD, and analysed with Framework to produce a draft health state descriptive system for HRQoL in DMD. In the second stage (refining the descriptive system), patients, clinicians and primary caregivers of people with DMD will assess the face validity of the descriptive system. This will be followed by a quantitative survey on a larger sample of patients, which will be analysed with psychometric analyses to produce a refined descriptive system. In the third stage (valuation and econometric modelling) an online discrete choice experiment with duration (DCE<sub>TTO</sub>) will be administered to a general public sample to generate utility values for the new measure.

### Ethics and dissemination

This study has received ethical approval from the NHS (REC reference: 18/SW/0055). The primary output of this research will be a condition-specific PBM (or 'bolt-on' to an existing generic PBM) in people with DMD and an associated value set. Results will be disseminated through international conferences and open-access journals.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This study will produce a systematic health state descriptive system for describing HRQoL in people with DMD using complementary mixed methods.
- The primary output of the study will be the first condition-specific PBM of HRQoL in people with DMD, which can be used in cost-effectiveness evaluations of new interventions.
- The study features input from a multidisciplinary team working with the charity Duchenne UK, clinicians, patients, and primary caregivers of people with DMD.
- Sample sizes in some parts of the study (quantitative patient surveys) will be acceptable but may be lower than optimal due to DMD being a rare disease.
- The design and validity of the measure and accompanying value set are restricted to the UK, and will not be demonstrated internationally without further study.

## INTRODUCTION

Duchenne muscular dystrophy (DMD) is an inherited neuromuscular disorder that predominantly affects boys and men. It has an estimated incidence of 1:3800 to 1:6300 in live births.[1] The disease causes progressive muscle weakness due to an absence of the dystrophin protein, which functions to help keep muscle cells intact. Diagnostic symptoms and functional impairment are evident from as early as two years old and average life expectancy of people with DMD is approximately 25 years,[2] although increasingly people with DMD are surviving into their fourth and even fifth decades.[3] The disease progresses through four recognised clinical stages characterised by increased muscle weakness, impaired ambulation and motor functioning, and cardiovascular and respiratory problems.[4] There is no known cure for the disease. Current clinical efforts are thus focused on improving the health-related quality of life (HRQoL) of people with DMD, and health interventions are necessarily evaluated for their cost effectiveness against this objective.

The most common form of economic evaluation of health interventions is cost utility analysis, which is used to compare interventions based on their cost per quality-adjusted life year (QALY).[5] The QALY is a single measure that combines information on changes in both quantity of life and HRQoL, and is required by the National Institute for Health and Care Excellence (NICE) in the UK during health technology assessment.[6] In order to derive a QALY, utilities (or preference weights) for different health states are required, which are often obtained from generic preference-based measures (PBMs) of health. Preference-based measures of health have two components: a health state descriptive system that can be used to describe all possible different health states defined by a set of multi-level dimensions; and a set of utility weights (or value set) that represent the relative preferences people have for the different health states. Development of a PBM thus typically involves a mixed-methods approach: involving qualitative and subsequent quantitative psychometric methods

1  
2  
3 for the generation and validation of the descriptive system, and a valuation survey for the  
4  
5 value set.[5]  
6

7 Preference-based measures can either be generic, and designed for use across all  
8  
9 health conditions, or condition-specific. Previous PBMs used to assess HRQoL in DMD  
10  
11 have been generic, and have included the EuroQol-5-Dimensions (EQ-5D)[7-8] and the  
12  
13 Health Utilities Index (HUI)[9]. Generic measures are often recommended in the assessment  
14  
15 of health technologies, as they allow for relative comparisons across health conditions.  
16  
17 However, generic measures often lack the specificity to assess aspects of HRQoL that may be  
18  
19 especially important to a particular health condition, or group of health conditions. For  
20  
21 example, the EQ-5D may not adequately measure fatigue,[10-13], social participation,[11,  
22  
23 14-16] or dignity,[13, 17-18] which have been shown to be important aspects of HRQoL for  
24  
25 people with DMD. Those that have been designed for use in people with DMD, such as the  
26  
27 Quality of Life in Neuromuscular Disease (QoL-NMD) instrument,[19] are not preference-  
28  
29 based and thus cannot be used to generate QALYs directly. Moreover, different measures  
30  
31 may be used across different clinical stages of DMD and throughout the life-course, making  
32  
33 it difficult to compare estimates of HRQoL on a common index, which is desirable for use to  
34  
35 inform health technology assessment.  
36  
37  
38

39 This study has been designed to evaluate the content validity of three existing, well-  
40  
41 used generic PBMs of HRQoL (the EQ-5D for adults, or the EQ-5D-Y which is the youth  
42  
43 version; the HUI, based on the HUI2 and HUI3 classification systems; and the Child Health  
44  
45 Utility 9D [CHU-9D]), while generating the content for a new condition-specific PBM, or  
46  
47 condition-specific 'bolt-on' addition to an existing PBM, calibrated for assessing HRQoL in  
48  
49 people with DMD. Bolt-ons are additional dimensions added onto an existing measure where  
50  
51 there is a concern that the measure does not capture all important dimensions, but where the  
52  
53 existing dimensions including severity levels are appropriate.[20-22] As is typical in studies  
54  
55  
56  
57  
58  
59

1  
2  
3 that involve the development of patient-reported outcome measures,[23] this research  
4 involves mixed methods, and proceeds through three sequential stages.  
5  
6

7 In the first stage of concept elicitation, semi-structured qualitative interviews will be  
8 conducted with boys and men diagnosed with DMD and analysed to produce a draft health  
9 state descriptive system for HRQoL in DMD. In the second stage of refining the descriptive  
10 system, the face validity and the psychometric properties of a questionnaire derived from the  
11 draft descriptive system will be assessed and improved using mixed methods, in order to  
12 produce a refined descriptive system and questionnaire for measuring HRQoL in DMD. In  
13 the third and final stage of valuation and econometric modelling, a discrete choice experiment  
14 with duration (DCE<sub>TTO</sub>) will be used in a survey of the general public, where they will be  
15 asked to value health states selected from the refined health state descriptive system in order  
16 to derive the value set. This protocol outlines the design and methodology we will use in  
17 each of the three stages of the research (summarised in figure 1). The product will be a  
18 rigorous PBM, or bolt-on(s) to an existing PBM, of HRQoL in people with DMD for use in  
19 the economic evaluation of health interventions.  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34

35 This work is funded by the charity Duchenne UK and falls under the umbrella of  
36 ‘Project Hercules’ (Health Research Collaboration United in Leading Evidence Synthesis) led  
37 by the charity. It is designed to develop common tools and practices in health technology  
38 assessment for DMD to improve engagement between industry and international agencies  
39 such as NICE on decisions on which medicines and treatments to fund. This includes a need  
40 for a robust and valid preference-based HRQoL metric to use to assess the cost-effectiveness  
41 of treatments.  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51

## 52 **AIMS**

53  
54 This study has the following three aims:  
55  
56  
57  
58  
59  
60



1. Using both bottom-up (qualitative) and top-down (review) methods generate a draft descriptive system for measuring HRQoL in people with DMD.
2. Using face validity and psychometric analyses with patients with DMD, and their primary carers and clinicians, refine the initial draft descriptive system generated in (1) to produce a final, refined descriptive system, suitable for assessing HRQoL in DMD.
3. Design and conduct a valuation study using DCE<sub>TTO</sub>, with the adult UK general public to produce utility values for all health states defined by the descriptive system generated in (2).

## **METHODS AND ANALYSIS**

### **Stage 1 – concept elicitation**

#### **Study design and procedure**

##### *Development of a topic guide*

A topic guide, or ‘interview schedule’, will be used to help provide structure to the semi-structured qualitative interviews and ensure that all important a priori information on HRQoL in people with DMD is covered.[24] The topic guide will be informed by a rapid scoping review of the literature on HRQoL themes in DMD (unpublished review, 2018) and the content of the generic PBMs of HRQoL assessed in this study (i.e., the EQ-5D-Y/EQ-5D, HUI, and CHU-9D). Experts through experience, including clinicians and caregivers to people with DMD, will be asked to informally review the topic guide to evaluate its face validity and inclusivity, prior to the interviews. These experts will be identified by Duchenne UK, as part of Project Hercules advisory groups.

##### *Qualitative interviews*

Participants with a primary diagnosis of DMD will be sent an invitation to take part in a 60-minute semi-structure interview exploring the domains of their HRQoL. The semi-

1  
2  
3 structured topic guide ensures important topics of interest are covered, while allowing the  
4 flexibility for elaboration and follow-ups in the case of interesting or ambiguous points made  
5 by the interviewee.[24] Across a number of areas, participants will be asked about their  
6 HRQoL and whether the EQ-5D-Y/EQ-5D, HUI, or CHU-9D adequately captures this  
7 dimension. Participants will also be asked to provide details on any dimensions of HRQoL  
8 that are important to them but are not covered in the topic guide.  
9

10  
11  
12  
13  
14  
15  
16 Participants will be sent a study pack directly by post from a recruiting NHS site (see  
17 below), but will have to contact the research team should they wish to take part. The study  
18 pack will contain an invitation letter, information sheet, consent form, background details  
19 form, and interview schedule. This content allows the participant to familiarise themselves  
20 with the material, and thus maximise the quality of subsequent interview data and informed  
21 consent of what is involved.[25] Participants will also be given a template notification letter  
22 for their GP, which they can pass on if and when they decide to disclose their participation in  
23 the study to their GP.  
24  
25  
26  
27  
28  
29  
30  
31  
32

33 To facilitate inclusivity, interviews will take place in the preferred location/medium  
34 and time for the participant. Interviews could thus take place face-to-face on NHS sites,  
35 University premises, participants' homes, and remotely via the telephone and Skype, where  
36 necessary (tools like Skype have been shown to be a valid alternative to face-to-face  
37 interviews in qualitative methods).[26] While it is preferred that the interviews take place  
38 with the participants alone (to avoid biased responses), the presence of others, such as a  
39 caregiver, and/or parent(s) and guardian(s) in the case of children (under 16 years old), will  
40 be facilitated on the participant's and/or consenting parent's wishes. In all cases with  
41 children, the parent or guardian will be asked to remain in the vicinity of the interview (i.e. in  
42 the same building). Participants, or a parent/guardian in the case of children, will give their  
43 informed consent prior to data collection, using a consent form. All interviews will be  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 digitally recorded on an encrypted device, transcribed verbatim by the research team, and  
4 anonymised. As well as taking part in an interview, participants will complete a brief  
5  
6 background details form, indicating some broad clinical and background characteristics to  
7  
8 ensure we interview a sufficiently broad cross-section of people with DMD. All documents  
9  
10 and the study methodology have been approved by the Duchenne UK Project Hercules  
11  
12 advisory groups.  
13

### 14 15 *Producing a draft descriptive system*

16  
17  
18 The qualitative data will be analysed to produce themes, used to populate a draft  
19  
20 health state descriptive system of HRQoL in DMD. The draft descriptive system will be used  
21  
22 to generate multiple HRQoL items as part of a questionnaire to be administered in a patient  
23  
24 sample of people with DMD in Stage 2. The draft descriptive system will be circulated for  
25  
26 expert comments and feedback from Duchenne UK via the Project Hercules advisory groups.  
27  
28 As well as from participants themselves, by ‘member-checking’ the results to make sure they  
29  
30 are consistent with participants’ perspectives.[27] This methodology has been previously  
31  
32 applied by members of the research team to generate descriptive systems for PBMs in other  
33  
34 health conditions.[28-29] Assuming, as predicted, that generic PBMs (i.e. the EQ-5D-Y/EQ-  
35  
36 5D, HUI, and CHU-9D) are insufficient to capture all important domains uncovered by the  
37  
38 qualitative research, the research project will progress onto Stage 2. If, in the unlikely event  
39  
40 that, the generic PBMs capture all important domains of HRQoL to people with DMD, then  
41  
42 we would not continue with the latter stages of the research, and would instead inform all  
43  
44 relevant parties, including the relevant research ethics committee, and transparently report on  
45  
46 our findings as they have emerged.  
47  
48

### 49 50 **Study sample and recruitment**

51  
52 Participants for Stage 1 will be identified by NHS health care teams across five  
53  
54 collaborating sites in the UK that specialise in the care and treatment of children and/or adults  
55  
56  
57  
58  
59

1  
2  
3 with DMD. The sites will identify and contact potential participants directly with a study  
4 pack (without any disclosure of patient data to the research team). Participants will then need  
5 to contact the research team if they are interested in taking part. Potential participants will be  
6 purposively sampled, in order to ensure a sufficient degree of representation across age,  
7 lower and upper limb function, and respiratory function, as advised by families of people  
8 with DMD via Duchenne UK. An illustrative sampling framework is shown in table 1.  
9  
10 Recruitment will proceed in an iterative fashion, whereby these selection characteristics are  
11 monitored to ensure a good balance across them. Participants will be recruited to ensure  
12 coverage across the life course of people with DMD, from childhood to adulthood. A  
13 minimum age of 7 years has been applied, based on previous work suggesting children at this  
14 age are capable of reporting on aspects of their HRQoL.[30] The inclusion and exclusion  
15 criteria for each stage of the study are illustrated in table 2.

16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60  
The sample size for the qualitative research interviews will be determined by data saturation. Data saturation is achieved when no additional novel themes are emerging from interviews with participants and a sufficient number of participants with different characteristics (as defined above) have been interviewed. While it is impossible to determine the exact number of participants required to reach data saturation in advance, prior studies of patients' perspectives on HRQoL in different specific health conditions provide an informed estimate of between 30 and 60 people.[28-29] Assuming a 50% uptake rate from potential participants, each site will be asked to identify between 12 and 25 potential participants.

#### Data analysis plan

The interview transcripts in Stage 1 will be subjected to thematic content analysis using Framework, an approach developed in the context of applied policy research.[31] Briefly, Framework is a form of thematic content analysis that involves coding and identifying common categories emerging from the data, which are indexed and then grouped

**Table 1** An example sampling framework for a recruiting site, based on a maximum identified sample of 25 potential participants

| Sampling criteria               |   |   |   |   |   |       |
|---------------------------------|---|---|---|---|---|-------|
| Lower limb function             | ✓ | × | × | × | × |       |
| Gross upper limb function       | ✓ | ✓ | ✓ | × | × |       |
| Respiratory function            | ✓ | ✓ | × | ✓ | × |       |
| Age group                       |   |   |   |   |   | Total |
| Pre-adolescence (< 10 years)    | 2 | 2 | 0 | 0 | 0 | 4     |
| Early adolescence (10-14 years) | 2 | 2 | 1 | 1 | 0 | 6     |
| Late adolescence (15-19 years)  | 0 | 2 | 2 | 2 | 1 | 7     |
| Early adulthood (20-29 years)   | 0 | 0 | 1 | 2 | 2 | 5     |
| Middle adulthood (30-39 years)  | 0 | 0 | 0 | 0 | 2 | 2     |
| Late adulthood (> 39 years)     | 0 | 0 | 0 | 0 | 1 | 1     |

'Lower limb function' is based on the ability to walk independently without a mobility device; 'gross upper limb function' is based on the ability to raise a hand to mouth to eat/drink independently; 'respiratory function' is based on the absence of any ventilation. Cell counts are approximations.

**Table 2** Sample inclusion/exclusion criteria for the three study stages

|                 | Inclusion criteria   | Exclusion criteria   |
|-----------------|--|--|
| <b>Stage 1</b>  | Boys and men diagnosed with DMD  | Women with DMD or those with other forms of muscular dystrophy   |
|                 | Aged 7+ years old  | Aged < 7 years old   |
|                 | Fluent in English  | Unable to understand or speak English  |
|                 | Have the capacity to consent (or receive parental consent if < 16 years old)   | Lacking in the capacity to consent (or receive parental consent)   |
| <b>Stage 2a</b> | Same criteria as Stage 1 for patients  | Same criteria as Stage 1 for patients  |
|                 | Clinicians and caregivers of people with DMD, aged 18+ years old, fluent in English, possessing the capacity to consent  | People who are not clinicians or caregivers of people with DMD or clinicians and caregivers who do not meet the inclusion criteria   |
| <b>Stage 2b</b> | Same criteria as Stage 1 for patients  | Same criteria as Stage 1 for patients  |
|                 | Proxy or assisted reporting by people aged 18+ years old who have the appropriate authority to respond on behalf of a patient diagnosed with DMD, fluent in English, possessing the capacity to consent. | People who are not providing proxy or assisted reporting for, or do not have the appropriate authority to respond on behalf of, patients diagnosed with DMD, or those who do not meet the inclusion criteria |
| <b>Stage 3</b>  | Men and women from the UK general population   | People with a diagnosis of DMD or other forms of muscular dystrophy  |
|                 | Aged 18+ years old   | Aged < 18 years old  |
|                 | Fluent in English  | Unable to understand or speak English  |
|                 | Have the capacity to consent   | Lacking in the capacity to consent   |

DMD, Duchenne muscular dystrophy. Additional iterative sampling strata apply to the qualitative interviews to ensure sufficient breadth of coverage.

1  
2  
3 into themes (or attributes). Nvivo qualitative analysis software will be used to facilitate and  
4 manage the analysis. The trustworthiness (quality) of the qualitative analysis will be assured  
5 using the four criteria of trustworthiness, which includes ‘member-checking’.[27]  
6  
7

## 8 9 **Stage 2 – refining the descriptive system**

### 10 Study design and procedure

#### 11 *Stage 2a – ensuring face validity*

12  
13  
14 In Stage 2a, a small sample of patients with DMD, primary caregivers of people with  
15 DMD, and clinicians will be invited to assess the face validity of the draft descriptive system.  
16 They will be asked to complete a series of tasks to check that the questionnaire is suitable for  
17 administration in a larger sample (i.e. that it can be understood by all parties and makes sense,  
18 including the wording of instructions, items, and response options). This exercise will be  
19 completed in the presence of the researcher, and, to minimise participant burden, will be  
20 offered face-to-face or remotely (e.g. via Skype or telephone) as in the interviews for Stage 1.  
21 Participants (which includes patients who have taken part in Stage 1; see below) will be sent  
22 an information sheet and consent form in advance to give them time to decide whether or not  
23 to take part in the study. Participants will provide consent in the same way as that in Stage 1  
24 (above), and the same procedural details will apply.  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38

39 Following consent, participants will be asked to complete the draft questionnaire in  
40 the presence of the researcher (either physically or remotely) to check that they can fill it in  
41 accurately and understand it. Following this, participants will be asked to complete a ranking  
42 exercise to determine the ordering of the response levels for the questionnaire, and a  
43 ‘cognitive debriefing’ exercise (where participants are asked what they think the items mean)  
44 to ensure that the items are measuring what they are intended to. If any patients have not  
45 provided background details as part of an interview in Stage 1, this will also be included. In  
46 place of basic aggregate clinical background details, we will collect basic age (decade ranges)  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 and gender information from clinicians and primary caregivers of people with DMD to  
4 provide basic descriptive background on the sample. Participants will also be given a  
5 template notification letter for their GP which they can pass on if and when they decide to  
6 disclose their participation in the study to their GP. These methods have previously been  
7 used by members of the research team in developing condition-specific measures in other  
8 health conditions.[29, 32] This exercise will not be recorded, but anonymous notes will be  
9 taken by the researcher on potential modifications to the questionnaire to make it as fit-for-  
10 purpose and user friendly as possible. In total, the face validity exercise is expected to take  
11 approximately 30 minutes.  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21

### 22 *Stage 2b – quantitative surveying*

23  
24 In Stage 2b, quality of life items derived from the descriptive system developed in  
25 Stage 1 (refined as necessary in Stage 2a), and a selection of generic PBMs informed by the  
26 results of Stage 1 to facilitate comparability (e.g., the EQ-5D-Y/EQ-5D, HUI, and/or the  
27 CHU-9D), will be administered to as wide as possible a patient sample of people with DMD.  
28 Participants with a diagnosis of DMD will be invited to complete a survey online, or offline  
29 by request to the researchers for a paper copy. Potential participants will be sent a study pack  
30 directly by post from a recruiting NHS site (see below), or respond to adverts circulated by  
31 charities and support groups, co-ordinated by Duchenne UK. Participants will be required to  
32 read an information sheet, and provide their informed consent (or the consent of a parent or  
33 guardian in the case of children) prior to completing the survey. These documents will be  
34 enclosed with the invitation letter for participants, and made compulsory reading on the  
35 survey website prior to accessing the study measures. While self-reported responses are  
36 desirable, to facilitate inclusivity we will make the survey as accessible as possible to assisted  
37 self-report and proxy responders. Participants will be asked to note on the survey whether  
38 they are completing it themselves (self-report), with help from another (assisted self-report),  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 or someone is completing it on their behalf (proxy). It is anticipated that the survey will take  
4  
5 up to 10 minutes of participants' time.  
6

### 7 *Producing a refined health state descriptive system*

8  
9 The quantitative data from the surveys of people with DMD in Stage 2b will be  
10  
11 subjected to psychometric analyses (see below), along with expert input from the Project  
12  
13 Hercules advisory groups, to produce a final health state descriptive system.[33] Depending  
14  
15 on the results of Stage 1, Stage 2 and expert input, this will either form a new HRQoL  
16  
17 measure, or 'bolt-on' dimensions to an existing generic PBM, such as the EQ-5D-Y/EQ-5D,  
18  
19 HUI, or CHU-9D.  
20  
21

### 22 **Study sample and recruitment**

23  
24 In Stage 2a (face validity exercise), participants will be those patients that have taken  
25  
26 part in Stage 1 and have consented to being contacted for further research by the research  
27  
28 team, and clinicians and primary caregivers of people with DMD identified by Duchenne UK  
29  
30 via their advisory groups. This is a pilot activity designed to ensure the questionnaire is 'fit-  
31  
32 for-purpose' prior to administration in a larger sample. A total sample size of 30 participants,  
33  
34 composed of 10 clinicians, 10 primary caregivers of, and 10 people with, DMD, based on  
35  
36 similar previous face validity work.[32]  
37  
38

39  
40 In Stage 2b (quantitative patient survey), participants will be those that have taken  
41  
42 part in Stage 1 and have consented to being contacted for further research by the research  
43  
44 team; additional participants identified by the health care team; or additional participants  
45  
46 identified via advertisements circulated by DMD charities and support groups (co-ordinated  
47  
48 by Duchenne UK). The identification of potential participants by the health care team will  
49  
50 proceed in the same fashion as that in Stage 1 (with study packs provided to potential  
51  
52 participants in their care). The number which they identify will be as many as possible that  
53  
54 meet the inclusion or exclusion criteria, but this will be pre-agreed with sites to align with  
55  
56  
57  
58  
59  
60



1  
2  
3 capacity (with an optimal number of approximately 40 additional participants per site).  
4  
5 While similar prior studies have used samples of approximately 342 to 655 patients,[33-34]  
6  
7 as DMD is a rare health problem, it is important to recognise that such numbers may be  
8  
9 difficult to achieve in practice. Recent simulations have suggested that sample sizes of at  
10  
11 least 100 people and above produce stable estimates in Rasch analyses,[35] from which to  
12  
13 draw conclusions, and so we have set this as our target minimum sample size, while aiming  
14  
15 for an optimal sample of 300 people or greater.  
16

### 17 Data analysis plan

18  
19  
20 In Stage 2a, face validity will be assessed using ranking and debriefing exercises in a  
21  
22 small sample of DMD patients, primary caregivers, and clinicians. This will also involve  
23  
24 taking anonymous notes of the responses and making refinements to the draft questionnaire  
25  
26 as a result of feedback. Similar methods have been used to help develop condition-specific  
27  
28 measures for amblyopia and self-management in diabetes.[29, 32] Refinement of the  
29  
30 descriptive system in Stage 2b will involve factor analysis, Rasch analysis, and standard  
31  
32 psychometric analyses as used in previous work by members of this group, with the aim of  
33  
34 producing a health state descriptive system appropriate for measuring the HRQoL of people  
35  
36 with DMD.[33-34] Factor analysis will be used to examine domains. Rasch and standard  
37  
38 psychometric analyses will be used to examine differential item functioning across important  
39  
40 subgroups (where feasible given the sample size), item response distributions, item severity,  
41  
42 ability for items to discriminate by severity, whether item response options are ordered by  
43  
44 severity, and correlations between items. Alongside all previous results and analyses in the  
45  
46 study, this analysis will be used to ensure the best performing items remain in the final  
47  
48 measure used for valuation in stage 3.  
49  
50  
51

### 52 **Stage 3 – valuation and econometric modelling**

#### 53 Study design and procedure

54  
55  
56  
57  
58  
59  
60

### *Designing the discrete choice experiment*

An increasingly widely used preference elicitation technique for valuing health is the DCE<sub>TTO</sub>, which is a technique that can be conducted online and data can be modelled to generate utility values for all states defined by the descriptive system.[36-37] The technique asks respondents to choose between two profiles, where each profile is described using a severity level of each of the dimensions from the descriptive system, plus a duration level (based on remaining life expectancy). Respondents are asked to choose which profile they think is best. The duration attribute will be 1, 4, 7 and 10 years, as used in recent surveys.[37-38] Profiles will be selected for inclusion in the DCE<sub>TTO</sub> using a D-Optimal design using the specialist software NGene. Illogical combinations of the attributes will be identified and excluded from the design. The design will also select which profile appears as A or B, and the combinations of profiles that each respondent values. Based on the expected size of the descriptive system, 200 health profile combinations will be valued, and each respondent will undertake 10 tasks, leading to 50 observations per health profile combination. In the DCE<sub>TTO</sub>, respondents will be asked to imagine the hypothetical health profiles for themselves, and asked which they think is best. They will not be told the underlying health condition (DMD) or that the profile is typically experienced by children, which causes problems regarding people's willingness to sacrifice a reduction in life expectancy to improve the health of the child (which is the method the technique uses to generate utility values). This perspective has been taken in other child valuation surveys, including the UK valuation of the CHU-9D,[39] and the Netherlands valuation of the CHU-9D, which also used the DCE with duration technique conducted online.[38]

### *Conducting the discrete choice experiment*

In order to produce utility values for health states defined by the health state descriptive system, DCE<sub>TTO</sub> will be used in an online survey of 1000 members of the UK

1  
2  
3 adult general population. The adult general population was also used in the UK and  
4  
5 Netherlands valuation of the CHU-9D, and is consistent with the NICE methods guide for  
6  
7 valuation, where adult general population values are sought rather than patient values.[6]  
8  
9 Furthermore, the elicitation of child values presents a large number of challenges around  
10  
11 whether they are cognitively able to undertake health state valuation tasks and little research  
12  
13 has been undertaken on this.[40] The survey will be hosted on Qualtrics, survey software  
14  
15 supported at the host research institution. Participants will read an information sheet online  
16  
17 and provide their informed consent online at the start of the survey. The survey will have  
18  
19 three parts. First participants will complete questions about themselves and their health,  
20  
21 second they will complete one practice question and 10 DCE<sub>TTO</sub> questions, and finally they  
22  
23 will report what they thought of the survey. Participants successfully completing the survey  
24  
25 will receive a pre-determined reward from the market research agency in line with the  
26  
27 agencies usual procedure.  
28  
29

### 30 *Valuation using the discrete choice experiment*

31  
32  
33 Health states will be valued using the DCE<sub>TTO</sub> data derived from the online survey  
34  
35 using standard regression techniques (see below). This exercise will produce utility values  
36  
37 for each (health state) attribute level defined by the condition-specific PBM of HRQoL in  
38  
39 DMD, for use in cost-effectiveness evaluations of new interventions.  
40

### 41 **Study sample and recruitment**

42  
43  
44 Identification and recruitment of the sample for Stage 3 will be outsourced to a  
45  
46 reputable market research company that conforms to governance standards (e.g. the Market  
47  
48 Research Society Code of Conduct). Participants will be invited to take part in the survey  
49  
50 through email or via a portal by the market research agency with a link to the online survey.  
51  
52 This method of recruitment has been used successfully by members of the research team on  
53  
54 previous health valuation projects.[38, 41] A pre-determined sample size of 1,000 people  
55  
56  
57  
58  
59

1  
2  
3 from the general population will be used. This sample size has been selected to ensure that  
4 each pair of health profiles is valued well in excess of a minimum of 20 times and a minimum  
5 of one pair of profiles per parameter estimated is selected in the regression model.[42]  
6  
7

### 8 9 Data analysis plan

10  
11 The DCE<sub>TTO</sub> surveys completed in Stage 3 will be analysed by regression analysis to  
12 produce utility values for health states defined by the health state descriptive system.[36]  
13

14 The utility value of each level of each attribute is generated using the ‘marginal rate of  
15 substitution’, generated by dividing the coefficient for each level of each attribute by the  
16 coefficient for duration, producing the utility value for each (health state) attribute level.  
17

18 Choices will be modelled using the conditional logistic model. Sensitivity analysis will be  
19 undertaken to assess the robustness of the results by excluding respondents. Similar methods  
20 have been used elsewhere by this group.[38, 41]  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30

### 31 ETHICS AND DISSEMINATION

32  
33 This study has been ethically reviewed and received Health Research Authority  
34 approval and a favourable ethical opinion from the NHS South West – Central Bristol  
35 Research Ethics Committee (REC reference: 18/SW/0055) on 14th March 2018. The work  
36 will be conducted in accordance with the ethical principles underlying the Declaration of  
37 Helsinki and good practice guidelines on the proper conduct of research. A full data  
38 management plan is in place to ensure the appropriate handling and use of personal and non-  
39 identifiable data, necessary for the successful conduct of this research. Advisory groups, in  
40 the form of steering and Public and Patient Involvement (PPI) groups, are being set-up by  
41 Duchenne UK as part of Project Hercules to help advise and oversee the findings that emerge  
42 from the research, including advising on ethical and practical issues such as patient burden.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

All study documents and the study methodology have been approved by Duchenne UK and parents of patients with DMD.

The primary output of this research will be a condition-specific PBM (or bolt-on to an existing measure) for assessing HRQoL in people with DMD, and an associated value set for use in cost-effectiveness evaluations. The results of this project will be disseminated via at least two international conferences and two journal manuscripts (i.e. one for Stages 1/2 and one for Stage 3). The manuscripts will be published open access to ensure the findings of the research are freely available, transparent and accessible to all with an interest in reading about them. Non-technical report(s) of the findings will also be circulated to study stakeholders via Duchenne UK.

## REFERENCES

1. Mendell JR, Shilling C, Leslie ND, et al. Evidence-based path to newborn screening for Duchenne Muscular Dystrophy. *Ann Neurol* 2012;71:304-313. doi:  
<http://dx.doi.org/10.1002/ana.23528>
2. Strehle EM, Straub V. Recent advances in the management of Duchenne muscular dystrophy. *Arch Dis Child* 2015;100:1173-1177. doi:  
<http://dx.doi.org/10.1136/archdischild-2014-307962>
3. Kieny PI, Chollet S, Delalande P, et al. Evolution of life expectancy of patients with Duchenne Muscular Dystrophy at AFM Yolaine de Kepper centre between 1981 and 2011. *Ann Phys Rehabil Med* 2013;56:443-54. doi:  
<http://dx.doi.org/10.1016/j.rehab.2013.06.002>
4. Landfeldt E, Lindgren P, Bell CF, et al. Compliance to care guidelines for Duchenne muscular dystrophy. *J Neuromuscul Dis* 2015;2:63-72. doi:  
<http://dx.doi.org/10.3233/JND-140053>

5. Brazier J, Ratcliffe J, Salomon JA, et al. *Measuring and valuing health benefits for economic evaluation*. Oxford, UK: Oxford University Press, 2017.
6. NICE (National Institute for Health and Care Excellence). *Guide to the methods of technology appraisal*. London, UK: NICE, 2013.
7. Cavazza M, Kodra Y, Armeni P, et al. Social/economic costs and health-related quality of life in patients with Duchenne muscular dystrophy in Europe. *Eur J Health Econ* 2016;17 Suppl 1:19-29. doi: <http://dx.doi.org/10.1007/s10198-016-0782-5>
8. Landfeldt E, Lindgren P, Bell CF, et al. Quantifying the burden of caregiving in Duchenne muscular dystrophy. *J Neurol* 2016;263:906-915. doi: <http://dx.doi.org/10.1007/s00415-016-8080-9>
9. Landfeldt E, Lindgren P, Bell CF, et al. Health-related quality of life in patients with Duchenne muscular dystrophy: a multinational, cross-sectional study. *Dev Med Child Neurol* 2016;58:508-515. doi: <http://dx.doi.org/10.1111/dmcn.12938>
10. Houwen-van Opstal SL, Jansen M, van Alfen N, et al. Health-related quality of life and its relation to disease severity in boys with Duchenne muscular dystrophy: satisfied boys, worrying parents--a case-control study. *J Child Neurol* 2014;29:1486-95. doi: <http://dx.doi.org/10.1177/088307381350649044>
11. Pangalila RF, van den Bos GA, Bartels B, et al. Prevalence of fatigue, pain, and affective disorders in adults with duchenne muscular dystrophy and their associations with quality of life. *Arch Phys Med Rehabil* 2015;96:1242-7. doi: <http://dx.doi.org/10.1016/j.apmr.2015.02.012>
12. Wei Y, Speechley KN, Zou G, et al. Factors Associated With Health-Related Quality of Life in Children With Duchenne Muscular Dystrophy. *J Child Neurol* 2016;31:879-86. doi: <http://dx.doi.org/10.1177/088307381562787955>

- 1  
2  
3 13. Wei S, Campbell C, Speechley K. Health-related quality of life in children with  
4  
5 Duchenne Muscular Dystrophy. *Can J Neurol Sci* 2014;41:S15.  
6  
7 14. Bendixen RM, Senesac C, Lott DJ, et al. Participation and quality of life in children with  
8  
9 Duchenne muscular dystrophy using the International Classification of Functioning,  
10  
11 Disability, and Health. *Health Qual Life Outcomes* 2012;10:43. doi:  
12  
13 <http://dx.doi.org/10.1186/1477-7525-10-43>  
14  
15 15. Bendixen RM, Lott DJ, Senesac C, et al. Participation in daily life activities and its  
16  
17 relationship to strength and functional measures in boys with Duchenne muscular  
18  
19 dystrophy. *Disabil Rehabil* 2014;36:1918-23. doi: 10.3109/09638288.2014.88344426  
20  
21 16. Heutinck L, Van Kampen N, Jansen M, et al. Physical activity in boys with DMD is  
22  
23 lower and less demanding compared to healthy boys. *Neuromuscul Disord*  
24  
25 2015;25:S303-S04. doi: <http://dx.doi.org/10.1016/j.nmd.2015.06.418>  
26  
27 17. Madsen A, Rahbek J, Werge B, et al. Living conditions and quality of life in adults with  
28  
29 Duchenne muscular dystrophy-A Danish survey. *Neuromuscul Disord* 2014;24:913. doi:  
30  
31 <http://dx.doi.org/10.1016/j.nmd.2014.06.39438>  
32  
33 18. Martinsen B, Dreyer P. Dependence on care experienced by people living with Duchenne  
34  
35 muscular dystrophy and spinal cord injury. *J Neurosci Nurs* 2012;44:82-90. doi:  
36  
37 10.1097/jnn.0b013e3182477a62  
38  
39 19. Dany A, Barbe C, Rapin A, et al. Construction of a Quality of Life Questionnaire for  
40  
41 slowly progressive neuromuscular disease. *Qual Life Res* 2015;24:2615-23. doi:  
42  
43 <http://dx.doi.org/10.1007/s11136-015-1013-8>  
44  
45 20. Finch AP, Brazier JE, Mukuria C, et al. An exploratory study on using principal-  
46  
47 component analysis and confirmatory factor analysis to identify bolt-on dimensions: The  
48  
49 EQ-5D case study. *Value Health* 2017;20:1362-1375. doi:  
50  
51 <http://dx.doi.org/10.1016/j.jval.2017.06.002>  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 21. Yang Y, Rowen D, Brazier J, et al. An exploratory study to test the impact on three  
4 “bolt-on” items to the EQ-5D. *Value Health* 2015;18:52-60. doi:  
5  
6 <http://dx.doi.org/10.1016/j.jval.2014.09.004>  
7  
8  
9 22. Yang Y, Brazier J, Tsuchiya A. Effect of adding a sleep dimension to the EQ-5D  
10 descriptive system: A “bolt-on” experiment. *Med Decis Making* 2014;34:42-53. doi:  
11  
12 <http://dx.doi.org/10.1177/0272989X13480428>  
13  
14  
15 23. Martin ML, Blum SI, Liedgens H, et al. Mixed-methods development of a new patient-  
16 reported outcome instrument for chronic low back pain: Part 1 – The patient assessment  
17 for low back pain – symptoms (PAL-S). *Pain* 2018; doi: [http://dx.doi.org/10.1097/j.pain.](http://dx.doi.org/10.1097/j.pain.0000000000001187)  
18  
19  
20  
21  
22  
23  
24 24. Stevens K, Palfreyman S. The use of qualitative methods in developing the descriptive  
25 systems of preference-based measures of health-related quality of life for use in  
26 economic evaluation. *Value Health* 2012;15:991-998. doi:  
27  
28 <http://dx.doi.org/10.1016/j.val.2012.08.2204>  
29  
30  
31  
32 25. Jepson M, Abbott D, Hastie J. “This is another personal question”: Research interviews  
33 and discussing sensitive issues with men with life-limiting conditions. *Int J Mens Health*  
34 2015;14:273-286. doi: <http://dx.doi.org/10.3149/jmh.1403.273>  
35  
36  
37  
38 26. Iacono VL, Symonds P, Brown DHK. Skype as a tool for qualitative research interviews.  
39 *Sociol Res Online* 2016; 21:12. doi: <http://dx.doi.org/10.5153/sro.3952>  
40  
41  
42  
43 27. Lincoln YS, Guba EG. *Naturalistic Inquiry*. Newbury Park: Sage, 1985  
44  
45 28. Carlton J. Identifying potential themes for the child amblyopia treatment questionnaire.  
46 *Optom Vis Sci* 2013;90:867-873. doi: <http://dx.doi.org/10.1097/OPX.0b013e318290cd7b>  
47  
48  
49 29. Carlton J, Elliott J, Rowen D, et al. Developing a questionnaire to determine the impact  
50 of self-management in diabetes: giving people with diabetes a voice. *Health Qual Life*  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60



- 1  
2  
3 30. Stevens K. Working with children to develop dimensions for a preference-based, generic,  
4 pediatric, health-related quality-of-life measure. *Qual Health Res* 2010; 20(3):340-351.  
5 doi: <http://dx.doi.org/10.1177/1049732309358328>  
6  
7  
8  
9 31. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman B  
10 Bryman, Burgess R, eds., *Analyzing Qualitative Data*. London: Routledge 1994;173-194.  
11  
12  
13 32. Carlton J. Developing the draft descriptive system for the child amblyopia treatment  
14 questionnaire (CAT-Qol): a mixed methods study. *Health Qual Life Outcomes*  
15 2013;11:174. doi: <http://dx.doi.org/10.1186/1477-7525-11-174>  
16  
17  
18 33. Carlon J. Refinement of the Child Amblyopia Treatment Questionnaire (CAT-QoL)  
19 using Rasch analysis. HEDS Discussion Paper No. 13.13. 2013; available at:  
20 [https://www.sheffield.ac.uk/polopoly\\_fs/1.321886!/file/13.13.pdf](https://www.sheffield.ac.uk/polopoly_fs/1.321886!/file/13.13.pdf)  
21  
22  
23 34. Rowen D, Brazier J, Young T. Deriving a preference-based measure for cancer using the  
24 EORTC QLQ-C30. *Value Health* 2011;14:721-731. doi:  
25 <http://dx.doi.org/10.1016/j.val.2011.01.004>  
26  
27  
28 35. Chen W-H, Lenderking W, Jin Y, et al. Is Rasch model analysis applicable in small  
29 sample size pilot studies for assessing item characteristics? An example using PROMIS  
30 pain behavior item back data. *Qual Life Res* 2014;23:485-493. doi:  
31 <http://dx.doi.org/10.1007/s11136-013-0487-5>  
32  
33  
34 36. Bansback N, Brazier J, Tsuchiya A, et al. Using a discrete choice experiment to estimate  
35 health state utility values. *J Health Econ* 2012;31:306-318. doi:  
36 <http://dx.doi.org/10.1016/j.jhealeco.2011.11.004>  
37  
38  
39 37. Norman R, Viney R, Brazier J, et al. Valuing SF-6D health states using a discrete choice  
40 experiment. *Med Decis Making* 2014;34:773-786. doi:  
41 <http://dx.doi.org/10.1177/0272989X13503499>  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 38. Rowen D, Mulhern B, Stevens K, et al. Estimating a Dutch value set for the paediatric  
4 preference-based CHU-9D using a discrete choice experiment with duration. *Value*  
5 *Health*, forthcoming.  
6  
7  
8  
9 39. Stevens K. Valuation of the Child Health Utility 9D Index. *Pharmacoeconomics* 2012;  
10 30:729-747. doi: <http://dx.doi.org/10.2165/11599120-000000000-00000>  
11  
12  
13 40. Stevens K. “Because that’s what matters to me”. A pilot study to test the feasibility and  
14 reliability of ordinal valuation methods for health state valuation with children. HEDS  
15 Discussion Paper, University of Sheffield 2015; available at:  
16 [https://www.sheffield.ac.uk/polopoly\\_fs/1.526959!/file/K.Stevens\\_The\\_feasibility\\_of\\_he](https://www.sheffield.ac.uk/polopoly_fs/1.526959!/file/K.Stevens_The_feasibility_of_health_state_valuation_by_children_DPfinal.pdf)  
17 [alth\\_state\\_valuation\\_by\\_children\\_DPfinal.pdf](https://www.sheffield.ac.uk/polopoly_fs/1.526959!/file/K.Stevens_The_feasibility_of_health_state_valuation_by_children_DPfinal.pdf)  
18  
19  
20  
21  
22  
23  
24 41. Rowen D, Stevens K, Labeit A, et al. Using a discrete choice experiment involving cost  
25 to value a classification system measuring the quality-of-life impact of self-management  
26 for diabetes. *Value Health* 2018;21:69-77. doi:  
27 <http://dx.doi.org/10.1016/j.jval.2017.06.016>  
28  
29  
30  
31  
32  
33 42. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare  
34 decision making. *Pharmacoeconomics* 2008;26:661-677. doi:  
35 <http://dx.doi.org/10.2165/00019053-200826080-00004>  
36  
37  
38  
39  
40  
41  
42

## 43 STATEMENTS

## 44 Acknowledgements

45 We would like to thank Dr Ros Quinlivan, Natalie Wilson, Dr Julie Woodley and members of  
46 the NHS South West – Central Bristol Research Ethics Committee, our collaborating health  
47 care sites, Duchenne UK, and the Project Hercules advisory groups for their ongoing input,  
48 feedback, and contributions into the design of this study.  
49  
50  
51  
52  
53  
54

## 55 Author statement

JC, DR, JB conceived the study; PAP, JC, DR contributed to the design of the study; PAP wrote the manuscript. All authors contributed to and approved the manuscript.

### **Funding statement**

This work was supported by Duchenne UK under the Project Hercules funding stream.

### **Competing interests statement**

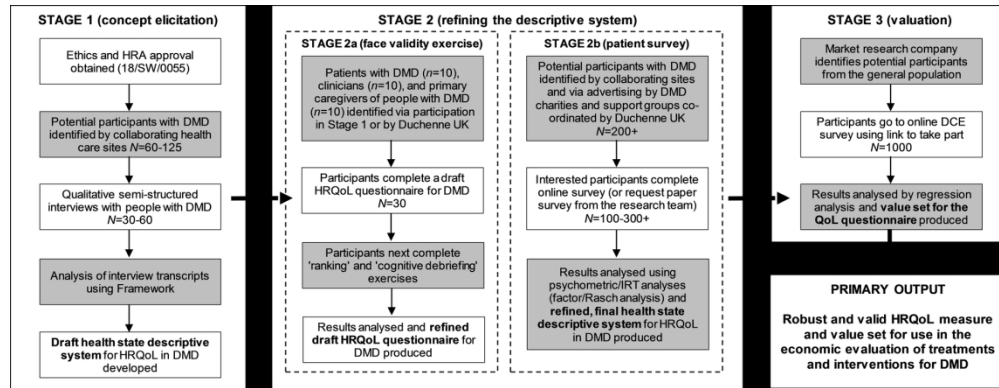
All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: all authors had financial support from Duchenne UK for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

### **Patient consent**

Obtained.

### **Ethics approval**

Ethical approval has been granted by the NHS South West – Central Bristol Research Ethics Committee (REC reference: 18/SW/0055).



Research project process diagram. Design stages omitted. DMD, Duchenne muscular dystrophy; DCE, discrete choice experiment; HRA, Health Research Authority; HRQoL, health-related quality of life.

166x64mm (300 x 300 DPI)

# BMJ Open

## PRODUCING A PREFERENCE-BASED QUALITY OF LIFE MEASURE FOR PEOPLE WITH DUCHENNE MUSCULAR DYSTROPHY: A MIXED-METHODS STUDY PROTOCOL

|                                 |  |
|---------------------------------|--|
| Journal:                        | <i>BMJ Open</i>  |
| Manuscript ID                   | bmjopen-2018-023685.R1   |
| Article Type:                   | Protocol   |
| Date Submitted by the Author:   | 06-Dec-2018  |
| Complete List of Authors:       | Powell, Philip; University of Sheffield, School of Health and Related Research; University of Sheffield, Economics<br>Carlton, Jill; University of Sheffield, School of Health and Related Research<br>Rowen, Donna; University of Sheffield, School of Health and Related Research<br>Brazier, John; University of Sheffield, School of Health and Related Research |
| <b>Primary Subject Heading</b>: | Health economics   |
| Secondary Subject Heading:      | Paediatrics, Qualitative research, Neurology   |
| Keywords:                       | Duchenne muscular dystrophy, Patient reported outcome measures, Psychometrics, QUALITATIVE RESEARCH, Quality of life   |
|                                 |  |

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8 **PRODUCING A PREFERENCE-BASED QUALITY OF LIFE MEASURE FOR**  
9  
10 **PEOPLE WITH DUCHENNE MUSCULAR DYSTROPHY: A MIXED-METHODS**  
11  
12 **STUDY PROTOCOL**  
13  
14  
15  
16

17 Philip A Powell,<sup>1,2\*</sup> Jill Carlton,<sup>1</sup> Donna Rowen,<sup>1</sup> John E Brazier<sup>1</sup>  
18  
19

- 20  
21  
22 1. Health Economics and Decision Science, School of Health and Related Research,  
23  
24 University of Sheffield, Sheffield, UK  
25  
26 2. Institute for Economic Analysis of Decision-making, Department of Economics,  
27  
28 University of Sheffield, Sheffield, UK  
29  
30  
31

32  
33 \* Correspondence to Philip A Powell, Health Economics and Decision Science, School of  
34  
35 Health and Related Research, University of Sheffield, Regent Court, 30 Regent Street,  
36  
37 Sheffield, UK, S1 4DA. Email: p.a.powell@sheffield.ac.uk. Tel: + 44 (0) 114 222 0794.  
38  
39  
40  
41

42 Word count (excluding title page, abstract, summary, references, figures and tables): 4936  
43  
44  
45

46  
47 Keywords: Duchenne Muscular Dystrophy; Patient Reported Outcome Measures;  
48  
49 Psychometrics; Qualitative Research; Quality of Life  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## ABSTRACT

### Introduction

Preference-based measures (PBMs) of health-related quality of life (HRQoL) are used to generate quality-adjusted life years, which are necessary for cost effectiveness evaluations of health interventions via cost utility analysis. These measures of health can be generic (i.e. pan-diagnostic) or condition-specific. No condition-specific PBM of HRQoL in Duchenne muscular dystrophy (DMD) exists, yet there are concerns that standard generic measures lack the specificity to assess aspects of HRQoL that are especially important to people with DMD. This study has been designed to produce a condition-specific PBM of HRQoL in DMD.

### Methods and analysis

This mixed-methods study proceeds through three stages. In the first stage (concept elicitation), semi-structured interviews will be conducted with boys and men diagnosed with DMD, and analysed with Framework to produce a draft health state descriptive system for HRQoL in DMD. In the second stage (refining the descriptive system), patients, clinicians and primary caregivers of people with DMD will assess the face validity of the descriptive system. This will be followed by a quantitative survey on a larger sample of patients, which will be analysed with psychometric analyses to produce a refined descriptive system. In the third stage (valuation and econometric modelling) an online discrete choice experiment with duration (DCE<sub>TTO</sub>) will be administered to a general public sample to generate utility values for the new measure.

### Ethics and dissemination

This study has received ethical approval from the NHS (REC reference: 18/SW/0055). The primary output of this research will be a condition-specific PBM (or 'bolt-on' to an existing generic PBM) in people with DMD and an associated value set. Results will be disseminated through international conferences and open-access journals.

## ARTICLE SUMMARY

### Strengths and limitations of this study

- This study will produce a systematic health state descriptive system for describing HRQoL in people with DMD using complementary mixed methods.
- The primary output of the study will be the first condition-specific PBM of HRQoL in people with DMD, which can be used in cost-effectiveness evaluations of new interventions.
- The study features input from a multidisciplinary team working with the charity Duchenne UK, clinicians, patients, and primary caregivers of people with DMD.
- Given the recruitment methods, there is likely to be some selection bias in the samples, and sample sizes in some parts of the study (quantitative patient surveys) will be acceptable but may be lower than optimal due to DMD being a rare disease.
- The design and validity of the measure and accompanying value set are restricted to the UK, and will not be demonstrated internationally without further study.



## INTRODUCTION

Duchenne muscular dystrophy (DMD) is an inherited neuromuscular disorder that predominantly affects boys and men. It has an estimated incidence of 1:3800 to 1:6300 in live births.[1] The disease causes progressive muscle weakness due to an absence of the dystrophin protein, which functions to help keep muscle cells intact. Diagnostic symptoms and functional impairment are evident from as early as two years old and average life expectancy of people with DMD is approximately 25 years,[2] although increasingly people with DMD are surviving into their fourth and even fifth decades.[3, 4] The disease progresses through four recognised clinical stages characterised by increased muscle weakness, impaired ambulation and motor functioning, and cardiovascular and respiratory problems.[5] There is no known cure for the disease. Current clinical efforts are thus focused on improving the health-related quality of life (HRQoL) of people with DMD, which is considerably lower than that expected in a state of perfect health.[4] Health interventions therefore are necessarily evaluated for their cost effectiveness in improving HRQoL. The most common form of economic evaluation of health interventions is cost utility analysis, which is used to compare interventions based on their cost per quality-adjusted life year (QALY).[6] The QALY is a single measure that combines information on changes in both quantity of life and HRQoL, and is required by the National Institute for Health and Care Excellence (NICE) in the UK during health technology assessment.[7] In order to derive a QALY, utilities (or preference weights) for different health states are required, which are often obtained from generic preference-based measures (PBM) of health. Preference-based measures of health have two components: a health state descriptive system that can be used to describe all possible different health states defined by a set of multi-level dimensions; and a set of utility weights (or value set) that represent the relative preferences people have for the different health states. Development of a PBM thus typically involves a mixed-methods approach:

1  
2  
3 involving qualitative and subsequent quantitative psychometric methods for the generation  
4 and validation of the descriptive system, and a valuation survey for the value set.[6]  
5  
6

7  
8 Preference-based measures can either be generic, and designed for use across all  
9 health conditions, or condition-specific. Previous PBMs used to assess HRQoL in DMD  
10 have been generic, and have included the EuroQol-5-Dimensions (EQ-5D)[8-9] and the  
11 Health Utilities Index (HUI)[10]. Generic measures are often recommended in the  
12 assessment of health technologies, as they allow for relative comparisons across health  
13 conditions. However, generic measures often lack the specificity to assess aspects of HRQoL  
14 that may be especially important to a particular health condition, or group of health  
15 conditions. For example, neither the EQ-5D nor the HUI appear to adequately measure  
16 fatigue,[11-14], social participation,[12, 15-17] or dignity,[14, 18-19] which have been  
17 shown to be important aspects of HRQoL for people with DMD. The HUI has a greater  
18 number of dimensions (and thus greater coverage) than the EQ-5D, and some limited  
19 research suggests the HUI may outperform the EQ-5D in people with disabilities, such as on  
20 proxy reliability.[20] However, the demonstration of adequate measurement properties of  
21 these generic PBMs in people with neurodisability is lacking.[21] Neither of these generic  
22 PBMs cover the full range of aspects of HRQoL that may be important to people with  
23 muscular dystrophies, including DMD.[22] This is problematic, as they have been used to  
24 generate HRQoL utilities for economic evaluations in DMD.[23] Quality of life measures  
25 that have been designed for use in people with DMD, such as the Quality of Life in  
26 Neuromuscular Disease (QoL-NMD) instrument,[24] are not preference-based and thus  
27 cannot be used to generate QALYs directly. Moreover, different measures may be used  
28 across different clinical stages of DMD and throughout the life-course, making it difficult to  
29 compare estimates of HRQoL on a common index, which is desirable for use to inform health  
30 technology assessment.  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

This study has been designed to evaluate the content validity of three existing, well-used generic PBMs of HRQoL (the EQ-5D for adults, or the EQ-5D-Y which is the youth version; the HUI, based on the HUI2 and HUI3 classification systems; and the Child Health Utility 9D [CHU-9D]), while generating the content for a new condition-specific PBM, or condition-specific ‘bolt-on’ addition to an existing PBM, calibrated for assessing HRQoL in people with DMD. Bolt-ons are additional dimensions added onto an existing measure where there is a concern that the measure does not capture all important dimensions, but where the existing dimensions including severity levels are appropriate.[25-27] As is typical in studies that involve the development of patient-reported outcome measures,[28] this research involves mixed methods, and proceeds through three sequential stages.

In the first stage of concept elicitation, semi-structured qualitative interviews will be conducted with boys and men diagnosed with DMD and analysed to produce a draft health state descriptive system for HRQoL in DMD. In the second stage of refining the descriptive system, the face validity and the psychometric properties of a questionnaire derived from the draft descriptive system will be assessed and improved using mixed methods, in order to produce a refined descriptive system and questionnaire for measuring HRQoL in DMD. In the third and final stage of valuation and econometric modelling, a discrete choice experiment with duration (DCE<sub>TTO</sub>) will be used in a survey of the general public, where they will be asked to value health states selected from the refined health state descriptive system in order to derive the value set. This protocol outlines the design and methodology we will use in each of the three stages of the research (summarised in figure 1). The product will be a rigorous PBM, or bolt-on(s) to an existing PBM, of HRQoL in people with DMD for use in the economic evaluation of health interventions.

This work is funded by the charity Duchenne UK and falls under the umbrella of ‘Project Hercules’ (Health Research Collaboration United in Leading Evidence Synthesis) led

1  
2  
3 by the charity. It is designed to develop common tools and practices in health technology  
4 assessment for DMD to improve engagement between industry and international agencies  
5 such as NICE on decisions on which medicines and treatments to fund. This includes a need  
6 for a robust and valid preference-based HRQoL metric to use to assess the cost-effectiveness  
7 of treatments.  
8  
9  
10  
11  
12  
13  
14  
15  
16

## 17 **AIMS**

18  
19 This study has the following three aims:

- 20  
21 1. Using both bottom-up (qualitative) and top-down (review) methods generate a draft  
22 descriptive system for measuring HRQoL in people with DMD.  
23
- 24  
25 2. Using face validity and psychometric analyses with patients with DMD, and their primary  
26 carers and clinicians, refine the initial draft descriptive system generated in (1) to produce  
27 a final, refined descriptive system, suitable for assessing HRQoL in DMD.  
28  
29  
30  
31  
32
- 33  
34 3. Design and conduct a valuation study using DCE<sub>TTO</sub>, with the adult UK general public to  
35 produce utility values for all health states defined by the descriptive system generated in  
36 (2).  
37  
38  
39  
40  
41

## 42 **METHODS AND ANALYSIS**

### 43 **Stage 1 – concept elicitation**

44  
45 Study design and procedure

#### 46 *Development of a topic guide*

47  
48 A topic guide, or ‘interview schedule’, will be used to help provide structure to the  
49 semi-structured qualitative interviews and ensure that all important a priori information on  
50 HRQoL in people with DMD is covered.[29] The topic guide will be informed by a rapid  
51 scoping review of the literature on HRQoL themes in DMD (unpublished review, 2018) and  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 the content of the generic PBMs of HRQoL assessed in this study (i.e., the EQ-5D-Y/EQ-5D,  
4 HUI, and CHU-9D). Experts through experience, including clinicians and caregivers to  
5 people with DMD, will be asked to informally review the topic guide to evaluate its face  
6 validity and inclusivity, prior to the interviews. These experts will be identified by Duchenne  
7 UK, as part of Project Hercules advisory groups. The selection of experts informing this  
8 project will be intended to generate a breadth of clinical expertise, but will ultimately be  
9 determined by convenience sampling (i.e. based on experts' availability in accordance with  
10 the project timelines).  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20

### 21 *Qualitative interviews*

22  
23  
24 Participants with a primary diagnosis of DMD will be sent an invitation to take part in  
25 a 60-minute semi-structure interview exploring the domains of their HRQoL. The semi-  
26 structured topic guide ensures important topics of interest are covered, while allowing the  
27 flexibility for elaboration and follow-ups in the case of interesting or ambiguous points made  
28 by the interviewee.[29] Across a number of areas, participants will be asked about their  
29 HRQoL and whether the EQ-5D-Y/EQ-5D, HUI, or CHU-9D adequately captures this  
30 dimension. Participants will also be asked to provide details on any dimensions of HRQoL  
31 that are important to them but are not covered in the topic guide.  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41

42 Participants will be sent a study pack directly by post from a recruiting NHS site (see  
43 below), but will have to contact the research team should they wish to take part. The study  
44 pack will contain an invitation letter, information sheet, consent form, background details  
45 form, and interview schedule. This content allows the participant to familiarise themselves  
46 with the material, and thus maximise the quality of subsequent interview data and informed  
47 consent of what is involved.[30] Participants will also be given a template notification letter  
48 for their GP, which they can pass on if and when they decide to disclose their participation in  
49 the study to their GP.  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 One experienced qualitative researcher will conduct the interviews to ensure  
4 consistency throughout. To facilitate inclusivity, interviews will take place in the preferred  
5 location/medium and time for the participant. Interviews could thus take place face-to-face  
6 on NHS sites, University premises, participants' homes, and remotely via the telephone and  
7 Skype, where necessary (tools like Skype have been shown to be a valid alternative to face-  
8 to-face interviews in qualitative methods).[31] While it is preferred that the interviews take  
9 place with the participants alone (to avoid biased responses), the presence of others, such as a  
10 caregiver, and/or parent(s) and guardian(s) in the case of children (under 16 years old), will  
11 be facilitated on the participant's and/or consenting parent's wishes. In all cases with  
12 children, the parent or guardian will be asked to remain in the vicinity of the interview (i.e. in  
13 the same building). Participants, or a parent/guardian in the case of children, will give their  
14 informed consent prior to data collection, using a consent form. All interviews will be  
15 digitally recorded on an encrypted device, transcribed verbatim by the research team, and  
16 anonymised. As well as taking part in an interview, participants will complete a brief  
17 background details form, indicating some broad clinical and background characteristics to  
18 ensure we interview a sufficiently broad cross-section of people with DMD. These  
19 background characteristics include brief questions on lower and upper limb mobility,  
20 ventilator use, use of steroid and heart medication, and age. All documents and the study  
21 methodology have been approved by the Duchenne UK Project Hercules advisory groups.

### 22 *Producing a draft descriptive system*

23  
24 The qualitative data will be analysed to produce themes, used to populate a draft  
25 health state descriptive system of HRQoL in DMD. The draft descriptive system will be used  
26 to generate multiple HRQoL items as part of a questionnaire to be administered in a patient  
27 sample of people with DMD in Stage 2. The draft descriptive system will be circulated for  
28 expert comments and feedback from Duchenne UK via the Project Hercules advisory groups.

1  
2  
3 As well as from participants themselves, by ‘member-checking’ the results to make sure they  
4 are consistent with participants’ perspectives.[32] This methodology has been previously  
5 applied by members of the research team to generate descriptive systems for PBMs in other  
6 health conditions.[33-34] Assuming, as predicted, that generic PBMs (i.e. the EQ-5D-Y/EQ-  
7 5D, HUI, and CHU-9D) are insufficient to capture all important domains uncovered by the  
8 qualitative research, the research project will progress onto Stage 2. If, in the unlikely event  
9 that, the generic PBMs capture all important domains of HRQoL to people with DMD, then  
10 we would not continue with the latter stages of the research, and would instead inform all  
11 relevant parties, including the relevant research ethics committee, and transparently report on  
12 our findings as they have emerged.  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25

## 26 Study sample and recruitment

27  
28 Participants for Stage 1 will be identified by NHS health care teams across five  
29 collaborating sites in the UK that specialise in the care and treatment of children and/or adults  
30 with DMD. The sites will identify and contact potential participants directly with a study  
31 pack (without any disclosure of patient data to the research team). Participants will then need  
32 to contact the research team if they are interested in taking part. Potential participants will be  
33 purposively sampled, in order to ensure a sufficient degree of representation across age,  
34 lower and upper limb function, and respiratory function, as advised by families of people  
35 with DMD via Duchenne UK. An illustrative sampling framework is shown in table 1.  
36  
37 Recruitment will proceed in an iterative fashion, whereby these selection characteristics are  
38 monitored to ensure a good balance across them. Participants will be recruited to ensure  
39 coverage across the life course of people with DMD, from childhood to adulthood. A  
40 minimum age of 7 years has been applied, based on previous work suggesting children at this  
41 age are capable of reporting on aspects of their HRQoL.[35] The inclusion and exclusion  
42 criteria for each stage of the study are illustrated in table 2.  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

The sample size for the qualitative research interviews will be determined by data saturation. Data saturation is achieved when no additional novel themes are emerging from interviews with participants and a sufficient number of participants with different characteristics (as defined above) have been interviewed. While it is impossible to determine the exact number of participants required to reach data saturation in advance, prior studies of patients' perspectives on HRQoL in different specific health conditions provide an informed estimate of between 30 and 60 people.[33-34] Assuming a 50% uptake rate from potential participants, each site will be asked to identify between 12 and 25 potential participants.

### Data analysis plan

The interview transcripts in Stage 1 will be subjected to thematic content analysis using Framework, an approach developed in the context of applied policy research.[36] Briefly, Framework is a form of thematic content analysis that involves coding and identifying common categories emerging from the data, which are indexed and then grouped

**Table 1** An example sampling framework for a recruiting site, based on a maximum identified sample of 25 potential participants

| <b>Clinical criteria</b>        |   |   |   |   |   |              |
|---------------------------------|---|---|---|---|---|--------------|
| Lower limb function             | ✓ | × | × | × | × |              |
| Gross upper limb function       | ✓ | ✓ | ✓ | × | × |              |
| Respiratory function            | ✓ | ✓ | × | ✓ | × |              |
| <b>Age group</b>                |   |   |   |   |   | <b>Total</b> |
| Pre-adolescence (< 10 years)    | 2 | 2 | 0 | 0 | 0 | 4            |
| Early adolescence (10-14 years) | 2 | 2 | 1 | 1 | 0 | 6            |
| Late adolescence (15-19 years)  | 0 | 2 | 2 | 2 | 1 | 7            |
| Early adulthood (20-29 years)   | 0 | 0 | 1 | 2 | 2 | 5            |
| Middle adulthood (30-39 years)  | 0 | 0 | 0 | 0 | 2 | 2            |
| Late adulthood (> 39 years)     | 0 | 0 | 0 | 0 | 1 | 1            |

'Lower limb function' is based on the ability to walk independently without a mobility device; 'gross upper limb function' is based on the ability to raise a hand to mouth to eat/drink independently; 'respiratory function' is based on the absence of any ventilation. Cell counts represent cross tabulations between clinical criteria and age group, and are approximations.

**Table 2** Sample inclusion/exclusion criteria for the three study stages

| <b>Inclusion criteria</b> | <b>Exclusion criteria</b> |
|---------------------------|---------------------------|
|---------------------------|---------------------------|



|                 |  |   |
|-----------------|--|---|
| <b>Stage 1</b>  | Boys and men diagnosed with DMD  | Women with DMD or those with other forms of muscular dystrophy  |
|                 | Aged 7+ years old  | Aged < 7 years old  |
|                 | Fluent in English  | Unable to understand or speak English   |
|                 | Have the capacity to consent (or receive parental consent if < 16 years old)   | Lacking in the capacity to consent (or receive parental consent)  |
| <b>Stage 2a</b> | Same criteria as Stage 1 for patients  | Same criteria as Stage 1 for patients   |
|                 | Clinicians and caregivers of people with DMD, aged 18+ years old, fluent in English, possessing the capacity to consent  | People who are not clinicians or caregivers of people with DMD or clinicians and caregivers who do not meet the inclusion criteria  |
| <b>Stage 2b</b> | Same criteria as Stage 1 for patients  | Same criteria as Stage 1 for patients   |
|                 | Proxy or assisted reporting by people aged 18+ years old who have the appropriate authority to respond on behalf of a patient diagnosed with DMD, fluent in English, possessing the capacity to consent. | People who are not providing proxy or assisted reporting for, or do not have the appropriate authority to respond on behalf of, patients diagnosed with DMD, or those who do who do not meet the inclusion criteria |
| <b>Stage 3</b>  | Men and women from the UK general population   | People with a diagnosis of DMD or other forms of muscular dystrophy   |
|                 | Aged 18+ years old   | Aged < 18 years old   |
|                 | Fluent in English  | Unable to understand or speak English   |
|                 | Have the capacity to consent   | Lacking in the capacity to consent  |

DMD, Duchenne muscular dystrophy. Additional iterative sampling strata apply to the qualitative interviews to ensure sufficient breadth of coverage.

into themes (or attributes). Nvivo qualitative analysis software will be used to facilitate and manage the analysis. The trustworthiness (quality) of the qualitative analysis will be assured using the four criteria of trustworthiness, which includes 'member-checking'. [32] Stage 1 of the project is estimated to take approximately 12 months.

## **Stage 2 – refining the descriptive system**

### Study design and procedure

#### *Stage 2a – ensuring face validity*

In Stage 2a, a small sample of patients with DMD, primary caregivers of people with DMD, and clinicians will be invited to assess the face validity of the draft descriptive system. They will be asked to complete a series of tasks to check that the questionnaire is suitable for administration in a larger sample (i.e. that it can be understood by all parties and makes

1  
2  
3 sense, including the wording of instructions, items, and response options). This exercise will  
4  
5 be completed in the presence of the researcher, and, to minimise participant burden, will be  
6  
7 offered face-to-face or remotely (e.g. via Skype or telephone) as in the interviews for Stage 1.  
8  
9 Participants (which includes patients who have taken part in Stage 1; see below) will be sent  
10  
11 an information sheet and consent form in advance to give them time to decide whether or not  
12  
13 to take part in the study. Participants will provide consent in the same way as that in Stage 1  
14  
15 (above), and the same procedural details will apply.  
16  
17

18  
19 Following consent, participants will be asked to complete the draft questionnaire in  
20  
21 the presence of the researcher (either physically or remotely) to check that they can fill it in  
22  
23 accurately and understand it. Following this, participants will be asked to complete a ranking  
24  
25 exercise to determine the ordering of the response levels for the questionnaire, and a  
26  
27 ‘cognitive debriefing’ exercise (where participants are asked what they think the items mean)  
28  
29 to ensure that the items are measuring what they are intended to. If any patients have not  
30  
31 provided background details as part of an interview in Stage 1, this will also be included. In  
32  
33 place of basic aggregate clinical background details, we will collect basic age (decade ranges)  
34  
35 and gender information from clinicians and primary caregivers of people with DMD to  
36  
37 provide basic descriptive background on the sample. Participants will also be given a  
38  
39 template notification letter for their GP which they can pass on if and when they decide to  
40  
41 disclose their participation in the study to their GP. These methods have previously been  
42  
43 used by members of the research team in developing condition-specific measures in other  
44  
45 health conditions.[34, 37] This exercise will not be recorded, but anonymous notes will be  
46  
47 taken by the researcher on potential modifications to the questionnaire to make it as fit-for-  
48  
49 purpose and user friendly as possible. In total, the face validity exercise is expected to take  
50  
51 approximately 30 minutes.  
52  
53  
54  
55  
56

57  
58 *Stage 2b – quantitative surveying*  
59  
60

1  
2  
3 In Stage 2b, quality of life items derived from the descriptive system developed in  
4 Stage 1 (refined as necessary in Stage 2a), and a selection of generic PBMs informed by the  
5 results of Stage 1 to facilitate comparability (e.g., the EQ-5D-Y/EQ-5D, HUI, and/or the  
6 CHU-9D), will be administered to as wide as possible a patient sample of people with DMD.  
7  
8 Participants with a diagnosis of DMD will be invited to complete a survey online, or offline  
9  
10 by request to the researchers for a paper copy. Potential participants will be sent a study pack  
11  
12 directly by post from a recruiting NHS site (see below), or respond to adverts circulated by  
13  
14 charities and support groups, co-ordinated by Duchenne UK. Participants will be required to  
15  
16 read an information sheet, and provide their informed consent (or the consent of a parent or  
17  
18 guardian in the case of children) prior to completing the survey. These documents will be  
19  
20 enclosed with the invitation letter for participants, and made compulsory reading on the  
21  
22 survey website prior to accessing the study measures. While self-reported responses are  
23  
24 desirable, to facilitate inclusivity we will make the survey as accessible as possible to assisted  
25  
26 self-report and proxy responders. Participants will be asked to note on the survey whether  
27  
28 they are completing it themselves (self-report), with help from another (assisted self-report),  
29  
30 or someone is completing it on their behalf (proxy). It is anticipated that the survey will take  
31  
32 up to 10 minutes of participants' time.  
33  
34  
35  
36  
37  
38  
39  
40  
41

### 42 *Producing a refined health state descriptive system*

43  
44 The quantitative data from the surveys of people with DMD in Stage 2b will be  
45  
46 subjected to psychometric analyses (see below), along with expert input from the Project  
47  
48 Hercules advisory groups, to produce a final health state descriptive system.[38] Depending  
49  
50 on the results of Stage 1, Stage 2 and expert input, this will either form a new HRQoL  
51  
52 measure, or 'bolt-on' dimensions to an existing generic PBM, such as the EQ-5D-Y/EQ-5D,  
53  
54 HUI, or CHU-9D.  
55  
56

### 57 **Study sample and recruitment**

1  
2  
3 In Stage 2a (face validity exercise), participants will be those patients that have taken  
4 part in Stage 1 and have consented to being contacted for further research by the research  
5 team, and clinicians and primary caregivers of people with DMD identified by Duchenne UK  
6 via their advisory groups. This is a pilot activity designed to ensure the questionnaire is ‘fit-  
7 for-purpose’ prior to administration in a larger sample. A total sample size of 30 participants,  
8 composed of 10 clinicians, 10 primary caregivers of, and 10 people with, DMD, based on  
9 similar previous face validity work.[37] In the event that more than 10 people with DMD  
10 from Stage 1 have agreed to being contacted for further research, participants will be selected  
11 to ensure breadth across the Stage 1 sampling framework in (Table 1).  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

24 In Stage 2b (quantitative patient survey), participants will be those that have taken  
25 part in Stage 1 and have consented to being contacted for further research by the research  
26 team; additional participants identified by the health care team; or additional participants  
27 identified via advertisements circulated by DMD charities and support groups (co-ordinated  
28 by Duchenne UK). The identification of potential participants by the health care team will  
29 proceed in the same fashion as that in Stage 1 (with study packs provided to potential  
30 participants in their care). The number which they identify will be as many as possible that  
31 meet the inclusion or exclusion criteria, but this will be pre-agreed with sites to align with  
32 capacity (with an optimal number of approximately 40 additional participants per site).  
33 While similar prior studies have used samples of approximately 342 to 655 patients,[38-39]  
34 as DMD is a rare health problem, it is important to recognise that such numbers may be  
35 difficult to achieve in practice. Recent simulations have suggested that sample sizes of at  
36 least 100 people and above produce stable estimates in Rasch analyses,[40] from which to  
37 draw conclusions, and so we have set this as our target minimum sample size, while aiming  
38 for an optimal sample of 300 people or greater.  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57

58 **Data analysis plan**  
59  
60

1  
2  
3 In Stage 2a, face validity will be assessed using ranking and debriefing exercises in a  
4 small sample of DMD patients, primary caregivers, and clinicians. This will also involve  
5 taking anonymous notes of the responses and making refinements to the draft questionnaire  
6 as a result of feedback. Similar methods have been used to help develop condition-specific  
7 measures for amblyopia and self-management in diabetes.[34, 37] Refinement of the  
8 descriptive system in Stage 2b will involve factor analysis, Rasch analysis, and standard  
9 psychometric analyses as used in previous work by members of this group, with the aim of  
10 producing a health state descriptive system appropriate for measuring the HRQoL of people  
11 with DMD.[38-39] Factor analysis will be used to examine domains. Rasch and standard  
12 psychometric analyses will be used to examine differential item functioning across important  
13 subgroups (where feasible given the sample size), item response distributions, item severity,  
14 ability for items to discriminate by severity, whether item response options are ordered by  
15 severity, and correlations between items. In the assessment of items, these analyses will be  
16 combined based on prior pre-defined criteria used in previous measure development by this  
17 research group.[41] Alongside all previous results and analyses in the study, this  
18 psychometric analysis will be used to ensure the best performing items remain in the final  
19 measure used for valuation in stage 3. Stage 2 of the project is estimated to take  
20 approximately 4 months.

### 21 **Stage 3 – valuation and econometric modelling**

#### 22 **Study design and procedure**

##### 23 *Designing the discrete choice experiment*

24 An increasingly widely used preference elicitation technique for valuing health is the  
25 DCE<sub>TTO</sub>, which is a technique that can be conducted online and data can be modelled to  
26 generate utility values for all states defined by the descriptive system.[42-43] The technique  
27 asks respondents to choose between two profiles, where each profile is described using a  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 severity level of each of the dimensions from the descriptive system, plus a duration level  
4  
5 (based on remaining life expectancy). Respondents are asked to choose which profile they  
6  
7 think is best. The duration attribute will be 1, 4, 7 and 10 years, as used in recent  
8  
9 surveys.[43-44] Profiles will be selected for inclusion in the DCE<sub>TTO</sub> using a D-Optimal  
10  
11 design using the specialist software NGene. Illogical combinations of the attributes will be  
12  
13 identified and excluded from the design. The design will also select which profile appears as  
14  
15 A or B, and the combinations of profiles that each respondent values. Based on the expected  
16  
17 size of the descriptive system, 200 health profile combinations will be valued, and each  
18  
19 respondent will undertake 10 tasks, leading to 50 observations per health profile combination.  
20  
21 In the DCE<sub>TTO</sub>, respondents will be asked to imagine the hypothetical health profiles for  
22  
23 themselves, and asked which they think is best. They will not be told the underlying health  
24  
25 condition (DMD) or that the profile is typically experienced by children, which causes  
26  
27 problems regarding people's willingness to sacrifice a reduction in life expectancy to improve  
28  
29 the health of the child (which is the method the technique uses to generate utility values).  
30  
31 This perspective has been taken in other child valuation surveys, including the UK valuation  
32  
33 of the CHU-9D,[45] and the Netherlands valuation of the CHU-9D, which also used the DCE  
34  
35 with duration technique conducted online.[44]

### 36 37 38 39 40 41 42 *Conducting the discrete choice experiment*

43  
44  
45 In order to produce utility values for health states defined by the health state  
46  
47 descriptive system, DCE<sub>TTO</sub> will be used in an online survey of 1000 members of the UK  
48  
49 adult general population. The adult general population was also used in the UK and  
50  
51 Netherlands valuation of the CHU-9D, and is consistent with the NICE methods guide for  
52  
53 valuation, where adult general population values are sought rather than patient values.[7]  
54  
55 Furthermore, the elicitation of child values presents a large number of challenges around  
56  
57 whether they are cognitively able to undertake health state valuation tasks and little research  
58  
59  
60

1  
2  
3 has been undertaken on this.[46] The survey will be hosted on Qualtrics, survey software  
4 supported at the host research institution. Participants will read an information sheet online  
5 and provide their informed consent online at the start of the survey. The survey will have  
6 three parts. First participants will complete questions about themselves and their health,  
7 second they will complete one practice question and 10 DCE<sub>TTO</sub> questions, and finally they  
8 will report what they thought of the survey. Participants successfully completing the survey  
9 will receive a pre-determined reward from the market research agency in line with the  
10 agencies usual procedure.  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20

### 21 *Valuation using the discrete choice experiment*

22  
23  
24 Health states will be valued using the DCE<sub>TTO</sub> data derived from the online survey  
25 using standard regression techniques (see below). This exercise will produce utility values  
26 for each (health state) attribute level defined by the condition-specific PBM of HRQoL in  
27 DMD, for use in cost-effectiveness evaluations of new interventions.  
28  
29  
30  
31  
32

### 33 **Study sample and recruitment**

34  
35 Identification and recruitment of the sample for Stage 3 will be outsourced to a  
36 reputable market research company that conforms to governance standards (e.g. the Market  
37 Research Society Code of Conduct). Participants will be invited to take part in the survey  
38 through email or via a portal by the market research agency with a link to the online survey.  
39 This method of recruitment has been used successfully by members of the research team on  
40 previous health valuation projects.[44, 47] A pre-determined sample size of 1,000 people  
41 from the general population will be used. This sample size has been selected to ensure that  
42 each pair of health profiles is valued well in excess of a minimum of 20 times and a minimum  
43 of one pair of profiles per parameter estimated is selected in the regression model.[48]  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55

### 56 **Data analysis plan**

1  
2  
3 The DCE<sub>TO</sub> surveys completed in Stage 3 will be analysed by regression analysis to  
4 produce utility values for health states defined by the health state descriptive system.[42]  
5  
6 The utility value of each level of each attribute is generated using the ‘marginal rate of  
7 substitution’, generated by dividing the coefficient for each level of each attribute by the  
8 coefficient for duration, producing the utility value for each (health state) attribute level.  
9  
10 Choices will be modelled using the conditional logistic model. Sensitivity analysis will be  
11 undertaken to assess the robustness of the results by excluding respondents. Similar methods  
12 have been used elsewhere by this group.[44, 47] Stage 3 of the project is estimated to take  
13 approximately 4 months.  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23

### 24 **Patient and public involvement**

25  
26 This research was driven by a recognised need within the Duchenne community to  
27 better measure quality of life in people with DMD. At the outset, their views were  
28 represented by the charity Duchenne UK, which includes mothers of sons with DMD.  
29  
30 Duchenne UK, under the work stream of Project Hercules, have contributed to the design of  
31 the proposed project. There is an established patient and public involvement group, which  
32 includes adults with DMD and parents of children with DMD. The group will contribute as  
33 research peers at several key stages of the project, including Stage 1 and Stage 2 during item  
34 generation and item selection. The research findings will be disseminated to participants via  
35 Duchenne UK, through established communication channels with members of the Duchenne  
36 community, and a bespoke Project Hercules event scheduled for November 2019.  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48

### 49 **ETHICS AND DISSEMINATION**

50  
51 This study has been ethically reviewed and received Health Research Authority  
52 approval and a favourable ethical opinion from the NHS South West – Central Bristol  
53 Research Ethics Committee (REC reference: 18/SW/0055) on 14th March 2018. The work  
54 will be conducted in accordance with the ethical principles underlying the Declaration of  
55  
56  
57  
58  
59  
60



1  
2  
3 Helsinki and good practice guidelines on the proper conduct of research. A full data  
4  
5 management plan is in place to ensure the appropriate handling and use of personal and non-  
6  
7 identifiable data, necessary for the successful conduct of this research. Advisory groups, in  
8  
9 the form of steering and Public and Patient Involvement (PPI) groups, are being set-up by  
10  
11 Duchenne UK as part of Project Hercules to help advise and oversee the findings that emerge  
12  
13 from the research, including advising on ethical and practical issues such as patient burden.  
14  
15 All study documents and the study methodology have been approved by Duchenne UK and  
16  
17 parents of patients with DMD.  
18  
19

20  
21 The primary output of this research will be a condition-specific PBM (or bolt-on to an  
22  
23 existing measure) for assessing HRQoL in people with DMD, and an associated value set for  
24  
25 use in cost-effectiveness evaluations. The results of this project will be disseminated via at  
26  
27 least two international conferences and two journal manuscripts (i.e. one for Stages 1/2 and  
28  
29 one for Stage 3). The manuscripts will be published open access to ensure the findings of the  
30  
31 research are freely available, transparent and accessible to all with an interest in reading  
32  
33 about them. Non-technical report(s) of the findings will also be circulated to study  
34  
35 stakeholders via Duchenne UK.  
36  
37  
38  
39  
40  
41

## 42 REFERENCES

- 43  
44 1. Mendell JR, Shilling C, Leslie ND, et al. Evidence-based path to newborn screening for  
45  
46 Duchenne Muscular Dystrophy. *Ann Neurol* 2012;71:304-313. doi:  
47  
48 <http://dx.doi.org/10.1002/ana.23528>  
49  
50
- 51  
52 2. Strehle EM, Straub V. Recent advances in the management of Duchenne muscular  
53  
54 dystrophy. *Arch Dis Child* 2015;100:1173-1177. doi:  
55  
56 <http://dx.doi.org/10.1136/archdischild-2014-307962>  
57  
58  
59  
60

- 1  
2  
3 3. Kieny PI, Chollet S, Delalande P, et al. Evolution of life expectancy of patients with  
4  
5 Duchenne Muscular Dystrophy at AFM Yolaine de Kepper centre between 1981 and  
6  
7 2011. *Ann Phys Rehabil Med* 2013;56:443-54. doi:  
8  
9 <http://dx.doi.org/10.1016/j.rehab.2013.06.002>  
10  
11
- 12 4. Ryder S, Leadley RM, Armstrong N, et al. The burden, epidemiology, costs and  
13  
14 treatment for Duchenne muscular dystrophy: an evidence review. *Orphanet J Rare Dis*  
15  
16 2017;12:79. doi:<http://dx.doi.org/10.1186/s13023-017-0631-3>  
17  
18
- 19 5. Landfeldt E, Lindgren P, Bell CF, et al. Compliance to care guidelines for Duchenne  
20  
21 muscular dystrophy. *J Neuromuscul Dis* 2015;2:63-72. doi:  
22  
23 <http://dx.doi.org/10.3233/JND-140053>  
24  
25
- 26 6. Brazier J, Ratcliffe J, Salomon JA, et al. *Measuring and valuing health benefits for*  
27  
28 *economic evaluation*. Oxford, UK: Oxford University Press, 2017.  
29  
30
- 31 7. NICE (National Institute for Health and Care Excellence). *Guide to the methods of*  
32  
33 *technology appraisal*. London, UK: NICE, 2013.  
34  
35
- 36 8. Cavazza M, Kodra Y, Armeni P, et al. Social/economic costs and health-related quality  
37  
38 of life in patients with Duchenne muscular dystrophy in Europe. *Eur J Health Econ*  
39  
40 2016;17 Suppl 1:19-29. doi: <http://dx.doi.org/10.1007/s10198-016-0782-5>  
41  
42
- 43 9. Landfeldt E, Lindgren P, Bell CF, et al. Quantifying the burden of caregiving in  
44  
45 Duchenne muscular dystrophy. *J Neurol* 2016;263:906-915. doi:  
46  
47 <http://dx.doi.org/10.1007/s00415-016-8080-9>  
48  
49
- 50 10. Landfeldt E, Lindgren P, Bell CF, et al. Health-related quality of life in patients with  
51  
52 Duchenne muscular dystrophy: a multinational, cross-sectional study. *Dev Med Child*  
53  
54 *Neurol* 2016;58:508-515. doi: <http://dx.doi.org/10.1111/dmcn.12938>  
55  
56
- 57 11. Houwen-van Opstal SL, Jansen M, van Alfen N, et al. Health-related quality of life and  
58  
59 its relation to disease severity in boys with Duchenne muscular dystrophy: satisfied boys,  
60

- 1  
2  
3 worrying parents--a case-control study. *J Child Neurol* 2014;29:1486-95. doi:  
4  
5 <http://dx.doi.org/10.1177/088307381350649044>  
6  
7
- 8 12. Pangalila RF, van den Bos GA, Bartels B, et al. Prevalence of fatigue, pain, and affective  
9  
10 disorders in adults with duchenne muscular dystrophy and their associations with quality  
11  
12 of life. *Arch Phys Med Rehabil* 2015;96:1242-7. doi:  
13  
14 <http://dx.doi.org/10.1016/j.apmr.2015.02.012>  
15  
16
- 17 13. Wei Y, Speechley KN, Zou G, et al. Factors Associated With Health-Related Quality of  
18  
19 Life in Children With Duchenne Muscular Dystrophy. *J Child Neurol* 2016;31:879-86.  
20  
21 doi: <http://dx.doi.org/10.1177/088307381562787955>  
22  
23
- 24 14. Wei S, Campbell C, Speechley K. Health-related quality of life in children with  
25  
26 Duchenne Muscular Dystrophy. *Can J Neurol Sci* 2014;41:S15.  
27  
28
- 29 15. Bendixen RM, Senesac C, Lott DJ, et al. Participation and quality of life in children with  
30  
31 Duchenne muscular dystrophy using the International Classification of Functioning,  
32  
33 Disability, and Health. *Health Qual Life Outcomes* 2012;10:43. doi:  
34  
35 <http://dx.doi.org/10.1186/1477-7525-10-43>  
36  
37
- 38 16. Bendixen RM, Lott DJ, Senesac C, et al. Participation in daily life activities and its  
39  
40 relationship to strength and functional measures in boys with Duchenne muscular  
41  
42 dystrophy. *Disabil Rehabil* 2014;36:1918-23. doi: 10.3109/09638288.2014.88344426  
43  
44
- 45 17. Heutinck L, Van Kampen N, Jansen M, et al. Physical activity in boys with DMD is  
46  
47 lower and less demanding compared to healthy boys. *Neuromuscul Disord*  
48  
49 2015;25:S303-S04. doi: <http://dx.doi.org/10.1016/j.nmd.2015.06.418>  
50  
51
- 52 18. Madsen A, Rahbek J, Werge B, et al. Living conditions and quality of life in adults with  
53  
54 Duchenne muscular dystrophy-A Danish survey. *Neuromuscul Disord* 2014;24:913. doi:  
55  
56 <http://dx.doi.org/10.1016/j.nmd.2014.06.39438>  
57  
58  
59  
60

- 1  
2  
3 19. Martinsen B, Dreyer P. Dependence on care experienced by people living with Duchenne  
4 muscular dystrophy and spinal cord injury. *J Neurosci Nurs* 2012;44:82-90. doi:  
5  
6 10.1097/jnn.0b013e3182477a62  
7  
8  
9
- 10 20. Bray N, Noyes J, Harris N, et al. Measuring the health-related quality of life of children  
11 with impaired mobility: examining correlation and agreement between children and  
12 parent proxies. *BMC Res Notes* 2017;10:377. doi:[https://doi.org/10.1186/s13104-017-](https://doi.org/10.1186/s13104-017-2683-9)  
13  
14  
15  
16 2683-9  
17  
18
- 19 21. Janssens A, Rogers M, Gumm R, et al. Measurement properties of multidimensional  
20 patient-reported outcome measures in neurodisability: a systematic review of evaluation  
21 studies. *Dev Med Child Neurol* 2016;58:437-451. doi:<http://doi.org/10.1111/dmcn.12982>  
22  
23  
24  
25
- 26 22. Bann CM, Abresch RT, Biesecker B, et al. Measuring quality of life in muscular  
27 dystrophy. *Neurology* 2015;84:1034-1042.  
28  
29 doi:<http://doi.org/10.1212/WNL.0000000000001336>  
30  
31  
32
- 33 23. Landfeldt E, Alfredsson L, Straub V, et al. Economic evaluation in Duchenne Muscular  
34 Dystrophy: Model frameworks for cost-effectiveness analysis. *Pharmacoeconomics*  
35 2017;35:249-258. doi:<http://doi.org/10.1007/s40273-016-0461-5>  
36  
37  
38  
39
- 40 24. Dany A, Barbe C, Rapin A, et al. Construction of a Quality of Life Questionnaire for  
41 slowly progressive neuromuscular disease. *Qual Life Res* 2015;24:2615-23. doi:  
42  
43  
44  
45  
46 <http://dx.doi.org/10.1007/s11136-015-1013-8>
- 47 25. Finch AP, Brazier JE, Mukuria C, et al. An exploratory study on using principal-  
48 component analysis and confirmatory factor analysis to identify bolt-on dimensions: The  
49 EQ-5D case study. *Value Health* 2017;20:1362-1375. doi:  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60 <http://dx.doi.org/10.1016/j.jval.2017.06.002>

- 1  
2  
3 26. Yang Y, Rowen D, Brazier J, et al. An exploratory study to test the impact on three  
4 “bolt-on” items to the EQ-5D. *Value Health* 2015;18:52-60. doi:  
5  
6 <http://dx.doi.org/10.1016/j.jval.2014.09.004>  
7  
8  
9  
10 27. Yang Y, Brazier J, Tsuchiya A. Effect of adding a sleep dimension to the EQ-5D  
11 descriptive system: A “bolt-on” experiment. *Med Decis Making* 2014;34:42-53. doi:  
12  
13 <http://dx.doi.org/10.1177/0272989X13480428>  
14  
15  
16  
17 28. Martin ML, Blum SI, Liedgens H, et al. Mixed-methods development of a new patient-  
18 reported outcome instrument for chronic low back pain: Part 1 – The patient assessment  
19 for low back pain – symptoms (PAL-S). *Pain* 2018; doi: [http://dx.doi.org/10.1097/j.pain.](http://dx.doi.org/10.1097/j.pain.0000000000001187)  
20  
21  
22  
23  
24  
25  
26 29. Stevens K, Palfreyman S. The use of qualitative methods in developing the descriptive  
27 systems of preference-based measures of health-related quality of life for use in  
28 economic evaluation. *Value Health* 2012;15:991-998. doi:  
29  
30  
31  
32  
33 <http://dx.doi.org/10.1016/j.val.2012.08.2204>  
34  
35  
36 30. Jepson M, Abbott D, Hastie J. “This is another personal question”: Research interviews  
37 and discussing sensitive issues with men with life-limiting conditions. *Int J Mens Health*  
38 2015;14:273-286. doi: <http://dx.doi.org/10.3149/jmh.1403.273>  
39  
40  
41  
42 31. Iacono VL, Symonds P, Brown DHK. Skype as a tool for qualitative research interviews.  
43  
44  
45  
46  
47  
48  
49 32. Lincoln YS, Guba EG. *Naturalistic Inquiry*. Newbury Park: Sage, 1985  
50  
51  
52 33. Carlton J. Identifying potential themes for the child amblyopia treatment questionnaire.  
53  
54  
55  
56  
57  
58  
59 34. Carlton J, Elliott J, Rowen D, et al. Developing a questionnaire to determine the impact  
60 of self-management in diabetes: giving people with diabetes a voice. *Health Qual Life Outcomes* 2017;15:146. doi: <http://dx.doi.org/10.1186/s12955-017-0719-4>

- 1  
2  
3 35. Stevens K. Working with children to develop dimensions for a preference-based, generic,  
4 pediatric, health-related quality-of-life measure. *Qual Health Res* 2010; 20(3):340-351.  
5  
6 doi: <http://dx.doi.org/10.1177/1049732309358328>  
7  
8  
9  
10 36. Ritchie J, Spencer L. Qualitative data analysis for applied policy research. In: Bryman B  
11 Bryman, Burgess R, eds., *Analyzing Qualitative Data*. London: Routledge 1994;173-194.  
12  
13  
14 37. Carlton J. Developing the draft descriptive system for the child amblyopia treatment  
15 questionnaire (CAT-QoI): a mixed methods study. *Health Qual Life Outcomes*  
16  
17 2013;11:174. doi: <http://dx.doi.org/10.1186/1477-7525-11-174>  
18  
19  
20 38. Carlon J. Refinement of the Child Amblyopia Treatment Questionnaire (CAT-QoL)  
21 using Rasch analysis. HEDS Discussion Paper No. 13.13. 2013; available at:  
22  
23 [https://www.sheffield.ac.uk/polopoly\\_fs/1.321886!/file/13.13.pdf](https://www.sheffield.ac.uk/polopoly_fs/1.321886!/file/13.13.pdf)  
24  
25  
26 39. Rowen D, Brazier J, Young T. Deriving a preference-based measure for cancer using the  
27 EORTC QLQ-C30. *Value Health* 2011;14:721-731. doi:  
28  
29 <http://dx.doi.org/10.1016/j.val.2011.01.004>  
30  
31  
32 40. Chen W-H, Lenderking W, Jin Y, et al. Is Rasch model analysis applicable in small  
33 sample size pilot studies for assessing item characteristics? An example using PROMIS  
34 pain behavior item back data. *Qual Life Res* 2014;23:485-493. doi:  
35  
36 <http://dx.doi.org/10.1007/s11136-013-0487-5>  
37  
38  
39 41. Keetharuth AD, Buck ET, Acquadro C, et al. Integrating qualitative and quantitative data  
40 in the development of outcome measures: The case of the Recovering Quality of Life  
41 (ReQoL) measures in mental health populations. *Int J Environ Res Public Health*  
42  
43 2018;15:1342. doi:<http://dx.doi.org/10.3390/ijerph15071342>  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60
42. Bansback N, Brazier J, Tsuchiya A, et al. Using a discrete choice experiment to estimate health state utility values. *J Health Econ* 2012;31:306-318. doi:  
<http://dx.doi.org/10.1016/j.jhealeco.2011.11.004>
  43. Norman R, Viney R, Brazier J, et al. Valuing SF-6D health states using a discrete choice experiment. *Med Decis Making* 2014;34:773-786. doi:  
<http://dx.doi.org/10.1177/0272989X13503499>
  44. Rowen D, Mulhern B, Stevens K, et al. Estimating a Dutch value set for the paediatric preference-based CHU-9D using a discrete choice experiment with duration. *Value Health*, forthcoming.
  45. Stevens K. Valuation of the Child Health Utility 9D Index. *Pharmacoeconomics* 2012; 30:729-747. doi: <http://dx.doi.org/10.2165/11599120-000000000-00000>
  46. Stevens K. "Because that's what matters to me". A pilot study to test the feasibility and reliability of ordinal valuation methods for health state valuation with children. HEDS Discussion Paper, University of Sheffield 2015; available at:  
[https://www.sheffield.ac.uk/polopoly\\_fs/1.526959!/file/K.Stevens\\_The\\_feasibility\\_of\\_health\\_state\\_valuation\\_by\\_children\\_DPfinal.pdf](https://www.sheffield.ac.uk/polopoly_fs/1.526959!/file/K.Stevens_The_feasibility_of_health_state_valuation_by_children_DPfinal.pdf)
  47. Rowen D, Stevens K, Labeit A, et al. Using a discrete choice experiment involving cost to value a classification system measuring the quality-of-life impact of self-management for diabetes. *Value Health* 2018;21:69-77. doi:  
<http://dx.doi.org/10.1016/j.jval.2017.06.016>
  48. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making. *Pharmacoeconomics* 2008;26:661-677. doi:  
<http://dx.doi.org/10.2165/00019053-200826080-00004>

1  
2  
3 **Figure 1** Research project process diagram. Design stages omitted. DMD, Duchenne  
4 muscular dystrophy; DCE, discrete choice experiment; HRA, Health Research Authority;  
5  
6 HRQoL, health-related quality of life.  
7  
8  
9

## 10 11 12 13 **STATEMENTS**

### 14 15 **Acknowledgements**

16  
17 We would like to thank Dr Ros Quinlivan, Natalie Wilson, Dr Julie Woodley and members of  
18 the NHS South West – Central Bristol Research Ethics Committee, our collaborating health  
19 care sites, Duchenne UK, patient advisers, and the Project Hercules advisory groups for their  
20 ongoing input, feedback, and contributions into the design of this study.  
21  
22  
23  
24  
25

### 26 27 **Author statement**

28  
29 JC, DR, JB conceived the study; PAP, JC, DR contributed to the design of the study; PAP  
30 wrote the manuscript. All authors contributed to and approved the manuscript.  
31  
32

### 33 34 **Funding statement**

35  
36 This work was supported by Duchenne UK under the Project Hercules funding stream.  
37

### 38 39 **Competing interests statement**

40  
41 All authors have completed the ICMJE uniform disclosure form at  
42 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: all authors had financial support from  
43 Duchenne UK for the submitted work; no financial relationships with any organisations that  
44 might have an interest in the submitted work in the previous three years; no other  
45 relationships or activities that could appear to have influenced the submitted work.  
46  
47  
48  
49  
50

### 51 52 **Patient consent**

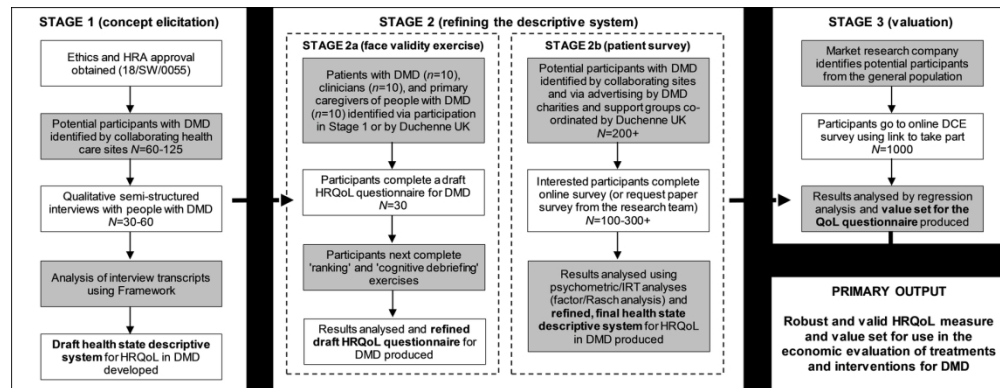
53  
54 Obtained.  
55

### 56 57 **Ethics approval**



1  
2  
3 Ethical approval has been granted by the NHS South West – Central Bristol Research Ethics  
4  
5 Committee (REC reference: 18/SW/0055).  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



Research project process diagram. Design stages omitted. DMD, Duchenne muscular dystrophy; DCE, discrete choice experiment; HRA, Health Research Authority; HRQoL, health-related quality of life.

166x64mm (300 x 300 DPI)