UK National Screening Committee

Newborn Screening for Duchenne Muscular Dystrophy

External review against programme appraisal criteria for the UK National Screening Committee (UK NSC)

Version: 5

Bazian Ltd.

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at http://www.screening.nhs.uk/policies and the policy review process is described in detail at http://www.screening.nhs.uk/policyreview

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Abbreviations List

6MWD - Six minute walking distance

6MWT - Six minute walking test

A6MCT - Assisted six minute cycling test

BMD - Becker muscular dystrophy

CBCL - Child Behaviour Checklist

CK - Creatine kinase

DBS - Dried blood spot

DMD - Duchenne muscular dystrophy

ESV - End Systolic Volume

LVESV - Left Ventricular End-Systolic Volume

MMT - Manual Muscle Testing

NBS - Newborn screening

NPV - Negative Predictive Value

PCR - Polymerase Chain Reaction

PKU - phenylketonuria

PPV - Positive predictive value

QMT – Quantitative Muscle Testing

RC - Reviewer calculated

RCT – Randomised controlled trial

RNA – Ribonucleic acid

SD – Standard Deviation

Plain English Summary

Condition

Duchenne muscular dystrophy (DMD) is a condition that affects 1 in 3,600 to 6,000 males born. DMD occurs as a result of altered genes that affect the body's ability to produce a certain type of protein called dystophin. The lack of this protein results in a decreased amount of muscle and strength. There is a similar but milder condition called Becker muscular dystrophy (BMD).

Most people with DMD are detected at around five years of age where their physical ability differs from other children. Signs like muscle weakness can sometimes be seen in people with DMD before this age. Without treatment muscle strength decreases and boys with DMD can develop problems with their breathing, bones and heart. Boys with DMD that are not treated are also likely to need a wheelchair before their teens and many die before 20 years of age.

Treatment

While it is not possible to completely cure DMD there are new drugs being tested that may help improve the amount of dystrophin protein produced in the body. Other drugs and treatments currently used can help improve the health and quality of life of sufferers.

Screening and Previous/ Current UK NSC Recommendations

Screening has been suggested as a way to identify children with DMD earlier. The most recent review of DMD in 2012 recommended against screening due to many uncertainties. This review searched for evidence since 2011. It focussed on the areas of the 2012 review that required further evidence or were unmet.

Findings

The review found a lack of evidence:

- for a reliable and appropriate screening strategy
- of any additional benefit from early treatment when people with DMD are identified during screening
- of what the best age for treatment to start and
- demonstrating wider effects or benefits from screening for DMD, such as on reproductive choices

Recommendation

The UKNSC does not recommend screening for Duchenne muscular dystrophy.

Executive Summary

Condition

Duchenne muscular dystrophy (DMD) is an X-linked disease that affects 1 in 3,600 to 6,000 live male births. DMD occurs as a result of mutations (mainly deletions) in the dystrophin gene which lead to an absence of or non-functional dystrophin protein, resulting in progressive muscle degeneration[1]. Mutations which lead to an abnormal but partly functional dystrophin protein can give rise to Becker muscular dystrophy (BMD), which has a milder clinical course than DMD.

Most DMD patients are diagnosed at around five years of age as this is when their physical ability differs from their peers. It can, however, cause mildly delayed motor milestones and muscle weakness prior to this age. Without treatment muscle strength deteriorates, and boys require the use of a wheelchair before their teens. Respiratory, orthopaedic, and cardiac complications emerge, and without intervention, average life expectancy is around 19 years. Non-progressive cognitive dysfunction may also be present.

Treatment

No curative treatments for DMD are currently available; however there have been recent developments in exon skipping treatments which show promise in allowing production of a partly functional dystrophin protein. Corticosteroid, respiratory, cardiac, orthopaedic, and rehabilitative interventions have led to improvements in function, quality of life, health, and longevity[1]. Treatments targeting known effects and complications could help patients to achieve a better life expectancy and quality of life.

Screening

Screening has been suggested in children with DMD to help identify and then manage the condition at an earlier stage. Existing treatment to manage the condition can lead to better function, quality of life, health, and longevity. Where screening has been undertaken, the initial screening test uses the newborn heel prick test to identify elevated creatine kinase (CK) activity levels.

Previous/ Current UK NSC Recommendations

The most recent UKNSC external review of DMD was published in 2012. This recommended against screening due to a number of uncertainties. Bazian Ltd were commissioned to undertake this rapid review, which considers whether the volume and direction of the evidence produced since the 2011 external review indicates that the previous recommendation should be reconsidered. Three main criteria will be considered, with particular focus given to areas the 2012 review identified as uncertain, or supported by insufficient evidence.

Findings

The review found a lack of evidence:

- For a reliable, high throughput screening strategy
- of any additional benefit from early treatment following screen detection or an optimum age for treatment initiation and
- demonstrating wider effects/benefits from screening for DMD, such as on reproductive choices

Recommendation

The UKNSC does not recommend screening for Duchenne muscular dystrophy. There remain uncertainties across key criteria and the evidence suggests that the recommendation not to screen for Duchenne muscular dystrophy should be retained.

Introduction

Duchenne Muscular Dystrophy

Duchenne muscular dystrophy (DMD) is an X-linked disease that affects 1 in 3,600 to 6,000 live male births.[1] DMD occurs as a result of mutations (mainly deletions) in the dystrophin gene which lead to an absence of or non-functional dystrophin protein, resulting in progressive muscle degeneration[1]. Mutations which lead to an abnormal but partly functional dystrophin protein can give rise to Becker muscular dystrophy (BMD), which has a milder clinical course than DMD. [2]

Most DMD patients are diagnosed at around 5 years of age as this is when their physical ability differs from their peers, but it can cause mildly delayed motor milestones and muscle weakness prior to this age. Without treatment muscle strength deteriorates, and most boys require the use of a wheelchair before their teens.[1] Respiratory, orthopaedic, and cardiac complications emerge, and without intervention, average life expectancy is around 19 years. Non-progressive cognitive dysfunction may also be present.

No curative treatments for DMD are currently available; however there have been recent developments in exon skipping treatments which show promise in allowing production of a partly functional dystrophin protein. Corticosteroid, respiratory, cardiac, orthopaedic, and rehabilitative interventions have led to improvements in function, quality of life, health, and longevity.[1]

Basis for current recommendation

The most recent UKNSC external review of DMD, published in 2012, concluded that the updated evidence published since 2004 did not support a change in national policy regarding newborn screening for DMD.

Several key uncertainties were highlighted by the 2012 evidence review. The need for further research into the screening test for DMD was a significant limitation, as the current test has been found to have a high false negative rate and a poor positive predictive value. In addition, there was insufficient evidence that identifying DMD in the newborn through screening improves long term outcomes in comparison to current practice. Other findings included the need for:

- Research to assess the optimal age of steroid initiation and optimum steroid regimen, as well as similar research regarding other treatments
- Comparison of outcomes between individuals identified by newborn screening for DMD in Wales and those identified at later ages from the remainder of the UK to identify any benefits and harms associated with earlier diagnosis through screening
- Audit of healthcare provision in the UK for patients with DMD to identify areas where provision needs to be optimised to meet the recommendations in the most recent guidance
- Further study of the natural history of newborns with the condition, potentially via the Welsh DMD screening programme

- More formal assessment of whether age at diagnosis could be lowered by improved clinical diagnosis
- Continued research into new treatments for DMD, including long term follow up to assess efficacy and safety
- Cost effectiveness analysis of newborn DMD screening

Current update review

The current review considers whether the volume and direction of the evidence produced since the 2012 external review indicates that the previous recommendation should be reconsidered. Four main criteria will be considered, with particular focus given to areas the 2012 review identified as uncertain, or supported by insufficient evidence. The main criteria and key questions reviewed are:

Table 1. Key questions for current DMD update review

Criterion	Key Questions (KQ)	# Studies Included
5. There should be a simple, safe, precise and validated screening test.	1) Is there any new evidence of a high volume/rapid throughput test that is suitable for whole population screening?	3
10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment	2a) Is there any new evidence since the last review of a treatment which seeks to alleviate the underlying protein defect in DMD or significantly improve symptoms/function?	17
	2b) Is there evidence that treatment following newborn screen adds any additional benefit in comparison with existing treatment pathways?	0
13(b) Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (e.g. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	3) Has any evidence been published since the last review that demonstrates wider effects/benefits from screening for DMD, such as on reproductive choices	0

A systematic literature search of studies published between the 1st January 2011 and 16th March 2015 yielded 1,488 references addressing DMD. Of these, 225 were assessed as being potentially relevant to the key questions outlined in Table 1. These studies were further filtered at title and abstract level, and 50 were selected for appraisal at full text. Conference abstracts were excluded. Each section below provides additional information on the evidence selection process for the given criterion.

Appraisal against UK NSC Criteria

These criteria are available online at http://www.screening.nhs.uk/criteria.

5. There should be a simple, safe, precise and validated screening test.

Testing for elevated levels of creatine kinase (CK) in newborn heel prick blood spot samples is the method usually used for newborn DMD screening.

CK activity is assessed through a bioluminescence or fluorescence assay, and those with raised levels may have a CK assay on a second dried blood sample or liquid blood to confirm initial results. Mutation analysis of the DMD gene would be used to confirm diagnosis.[3]

This test was reportedly first used to screen for muscular dystrophy in 1975.[3] Sample collection is relatively simple to perform as it is carried out using the newborn heel prick bloodspots that are currently collected for other newborn tests.

CK is elevated in the blood of boys with a DMD mutation due to the muscle damage that occurs as a result of the lack of dystrophin, rather than as a direct function of the gene defect.[4] Muscle damage from other causes can also increase CK levels in the blood. For example, birth trauma and the method of delivery can lead to transient increases in CK levels, which may increase the risk of false positives when testing newborn blood samples. [5]

The previous UK NSC update review reported unpublished data from the DMD screening programme conducted in Wales. It found the CK screening test performance to be poor in terms of having a high false negative rate (about 17%), and low positive predictive value (about 41%).

Due to the proven poor performance of the current CK test, other strategies need to be investigated, and are the focus of reporting here.

Current UKNSC key question

1) Is there any new evidence of a high volume/rapid throughput test that is suitable for whole population screening?

Description of the evidence

Fourteen studies were identified as potentially relevant during title and abstract sifting and were further assessed at full text. Diagnostic studies assessing test performance for detecting DMD (clinical validity), including reports of test performance in DMD screening programmes, were prioritised.

Of the 14 studies there were two[4, 6] relevant papers identified, one was a full publication of the Welsh Screening Programme of which similar data from personal communication was included in the previous review. The other study reported an alternative approache to screening for DMD.

This study used a two-tier system with dried blood spot analysis to first assess CK in newborns and follow up DMD gene testing on the same blood spot in those who screened positive rather than recalling all those with elevated CK measurements.[6]

Another study with some relevance assessed the use of muscle specific microRNAs as alternate biomarkers to monitor the progression of DMD and as potential diagnostic markers. MicroRNAs are a small non-coding molecule that functions in ribonucleic acid (RNA) silencing and post-transcriptional regulation of gene expression.

CK assay based screening

Two studies utilised CK assay based screening, and their results are contrasted in Table 2 below, followed by a summary of each study in the text.

Table 2: Results from DMD screening studies using total CK as a screening marker

First author Year Country	n=	Total CK Cut-off	Incidence of DMD	Sensitivity (%)	Specificity (%)	PPV (%)
Moat 2013[4] Wales	343,170	CK levels > 200U/l were retested in duplicate. If mean of triplicate results was >250U/l then clinical appointment and referral were arranged for serum CK testing, if CK levels were raised (not defined) further investigations (e.g. DNA testing, muscle biopsy) were considered	1:6,603	81.6	99.97	38.6
Mendell 2012[6] USA	37,649	Phase 2 ≥600U/l Phase 3 & 4 >750U/l Raised total CK prompted DNA testing of bloodspot.	1:6,275	NC	NC	NC

NC not calculable

The published report of the Welsh DMD screening programme covered data for 1990 to 2011, i.e. including one additional year not included in the unpublished data reported in the last UK NSC update review (which covered 1990 to 2010). This published report included the CK

screening results of 343,170 boys (unpublished data included screening results for 312,073 boys). Of these boys 145 had an average blood spot CK level ≥250U/L, and had follow up testing of CK levels at 6-8 weeks. At this point 79 boys were found to still have elevated CK levels.

Of the 79 boys with persistently elevated CK levels, 56 were found to have DMD, five had Becker muscular dystrophy and five were confirmed to have rarer forms of muscular dystrophy. By the end of the period assessed 13 boys who had screened negative for DMD were identified to have developed the condition. These boys received definitive diagnosis at a mean age of 4.33 years. Two cases of DMD were also diagnosed in boys whose parents had declined newborn screening.

Test accuracy statistics were similar to the unpublished data (reported in the previous review) with respect to:

- sensitivity (81.6%) and false negative rate (18.4%)
- specificity (99.97%) and false positive rate (0.03%)
- positive predictive value (38.6%).[4]

This large study offers a good representation of results which could be obtained with newborn DMD screening in a UK population using currently available methods. Another major strength was that it was carried out over a long period of time, which allowed looking for false negatives. The method of looking for false negatives was still opportunistic as it would not have been feasible to test the DNA of all babies, therefore it is possible additional false negatives exist who have not been identified.

A pilot screening programme was conducted in Ohio, USA, and consisted of four study phases (Phase 1: n=30,547, Phase 2: n=6,928, Phase 3: n=10,937 and Phase 4: n=19,884). The programme aimed to assess the performance of a 2-tiered method for DMD newborn screening (NBS) on dried blood spot (DBS), with initial screening for CK followed by DNA isolation and DMD gene analysis on the same dried blood spot of those who were screen positive following CK testing. This reduces the waiting time to take a second sample and addressed the concern that follow up of infants to retest venous blood several weeks after birth was impractical.

The study aimed to reduce the number of false positives that would be expected based on CK alone. In phase 3, using a CK threshold ≥750U/l, the CK test on its own was reported to have the lowest false positive rate (0.52%) compared to a threshold of ≥600U/l. This false positive rate was reported by the study itself, based on the findings of DNA testing in the screen positives, but this assumes that all of the newborns who screened negative were truly negative. However, without follow up or testing of screen-negative newborns it is not possible to say whether they are true negatives. Given the results in the Welsh screening programme, the possibility of false negatives cannot be ruled out.

In addition, the study did not carry out additional blood sample or family DNA testing on either all of the 'false positives', or all of those screened, meaning that the DMD status of all of those screening positive may not be accurate. Therefore, it was not possible to calculate specificity (Sp), sensitivity (Sn), positive predictive value (PPV) or negative predictive value (NPV) due to lack of data on the true DMD status of positive and negative tests.

The theory behind this approach was that as the DNA test was carried out on the same blood spot as the CK test, there would be no need to recall all newborns testing positive with CK test for further blood sampling, which would potentially reduce unnecessary concern among parents of babies with a false positive CK test result. However, in the pilot the researchers did request (and pay for) the primary care physician to obtain a repeat venous blood sample for CK testing any boys whose screened positive but for whom no DMD mutation was found on DNA testing of the bloodspot. Therefore there was still attempted re-testing of all screen positives, although uptake was low (only 26% of DNA test-negatives had follow-up samples tested). It was not clear whether this stage was only for the purposes of the pilot study (to look for false negatives from DNA testing), or intended to be a standard part of the screening process. If it was part of the screening process then the approach would not be likely to substantially reduce the number of repeat CK tests required or unnecessary concern among parents.

Two out of the 45 screen positives who did not have DMD mutations identified and did have repeat venous CK testing were reported to have "slightly elevated" CK levels (>500U/l) but whether these individuals had further DNA testing or diagnosis was not reported. Therefore it is not possible to know whether they were DNA-test false negatives.

The DNA testing of bloodspots for all initially raised CKs may have practical implications in terms of costs or need for equipment/staff to do DNA testing. In terms of applicability to the UK, this programme included newborns and assessed similar methods to those used in the Welsh screening programme (total CK testing plus DNA testing) in the UK. The main difference was that DNA testing was carried out on the bloodspots screening positive for raised CK level, without the need for a repeat venous blood CK test first. As this was a US population the findings may not be representative of the ethnic mix in the UK.

While the risk of bias was low in some areas, the study was at high risk of bias in areas relating to the confirming results with a reference standard. It did not carry out additional blood sample or family DNA testing on either all of the false positives, or all of those screened. There was also a lack of follow up of those screening negative on the CK test, meaning that false negatives are unlikely to have been detected. Given the high level of false negatives identified in the Welsh DMD screening programme this is a considerable limitation. It is not possible to confirm the performance of the two tiered bloodspot strategy as a whole (e.g. sensitivity, specificity, NPV or PPV) compared to normal screening procedure.

Discussion

A limited amount of new evidence was found on tests for DMD for whole population screening. One study reported on a pilot screening programme in the US using CK testing on newborn blood spot followed by DNA testing on the same blood spot if CK was elevated. This approach differed from the traditional DMD screening approach in carrying out the DNA testing on the same bloodspot, rather than repeat testing of CK on a venous blood sample to confirm elevation before DNA testing. The study population may not be generalisable to a UK population. The confirmatory diagnostic tests were conducted on screen positive samples only and therefore the true diagnostic status of those who were screen negative is uncertain. The lack of follow up on negative tests means we cannot be certain of the number of false negatives, and this may be

high just as in the Welsh programme. As such, key performance metrics (i.e. specificity, sensitivity, positive and negative predictive value) cannot be determined.

The only other study identified with some relevance assessed test performance of ability of muscle specific micro-RNAs to differentiate between DMD cases and controls.[7] This was an early stage study and it is unclear whether this method would be viable as a high volume throughput screening test due to the use of venous blood samples and the need to isolate RNA and carry out reverse transcriptase PCR. The study was not undertaken in a population which is generalisable to newborn screening.

Summary: Criterion 5 – Not met. There is evidence of poor performance of total CK as a marker for screening in a Welsh population. There was insufficient, high quality evidence of a new high volume/rapid throughput test suitable for whole population screening.

10. There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

The TREAT-NMD guidelines from 2010 report that pharmacological interventions have begun to change the natural history of DMD. DMD patients, who are usually diagnosed at around the age of 5 years, encounter a loss of strength and function and interventions such as corticosteroids and physical therapy can minimise these effects.[1]

Corticosteroid therapy is provided to DMD patients in order to maintain the ability to walk, and minimise risk of other later complications, such as scoliosis and cardiac decline.[1] There is no recommended age at which to start corticosteroid treatment, it is based on the individual's functional state and possible adverse events. This treatment is not recommended for males under two as the child would still be gaining motor skills. For patients who are no longer ambulatory corticosteroid treatment may be continued to reduce progression of scoliosis and delaying the decline in respiratory and cardiac function.

The previous UK NSC update review on DMD screening reported that there were no curative treatments available and none that had been shown to have a greater benefit when delivered to screen detected children. It did report that steroid treatment improves muscle function, but consensus recommendations advised that steroid treatment should be started before a child reached the plateau of motor development, which usually occurs between the age of 4 and 8 years. Given that median age for DMD diagnosis in the UK was reported to be about 4 years, and median age at initiation of corticosteroids about 6 years, it was unclear whether earlier diagnosis through screening would necessarily result in earlier steroid treatment or improved outcomes.

Until recently there have been no disease-modifying treatments for DMD patients. Recent developments have been new genetic therapies such as ataluren, drisapersen and eteplirsen that aim to modify disease progression by addressing the genetic defect causing DMD.

Ataluren is thought to work by allowing 'read-through' of any nonsense mutations. These mutations cause a premature stop in the dystrophin protein, leaving it incomplete. 'Read-through' of these mutations allows the premature stop command to be skipped and production of functional dystrophin protein to continue. Nonsense mutations affect approximately 13% of DMD cases.

Drisapersen and eteplirsen work in a different way. They are targeted specifically at patients with mutations in exon 51 of the dystrophin gene, who account for a further 13% of patients with DMD. They induce skipping of this exon, resulting in the production of functional but shortened dystrophin protein similar to that found in the less severe dystrophinopathy, Becker muscular dystrophy.[6] These two treatments will not work in individuals with mutations outside of exon 51.

A number of other drugs are currently in the development stage for patients with mutations in different exons.

Current UKNSC key question

2a) Is there any new evidence since the last review of a treatment which seeks to alleviate the underlying genetic defect causing DMD or significantly improve symptoms/function?

2b) Is there evidence that treatment following newborn screen adds any additional benefit in comparison with existing treatment pathways?

Description of the evidence

Thirty seven studies were identified as potentially relevant during title and abstract sifting and were further assessed at full text. Only systematic reviews and comparative studies were included.

Of the 37 studies identified 17 were included in the final analysis (13 randomised controlled trials, four non-randomised comparative studies). The main reasons for exclusion were that studies were non-comparative or reported as conference abstracts only.

No studies were found which assessed outcomes of treatment after screen detection of DMD.

2a) Is there any new evidence since the last review of a treatment which seeks to alleviate the underlying defect of DMD and/or significantly improve symptoms/function?

Results

Genetic (disease-modifying) treatments

Five studies[8-12] were identified which explored the use of genetic treatments for DMD. The studies assessed various outcomes such as change from baseline for six minute walking distance (6MWD), muscle strength, dystrophin levels, loss of ambulation and pharmacokinetic measures. Most studies were small in sample size, ranging from 12 to 174. Table 3 summarises the results

of these studies and also their marketing authorisation status. Results are also briefly summarised narratively in the text below.

Ataluren

Ataluren was assessed in two studies.[8, 9] Treatment was initiated in boys from age five. In one relatively large phase 2b trial (n=174) found that ataluren reduced the decline in walking ability after 48 weeks by almost 30 m compared with placebo. However, this difference did not reach statistical significance (intention to treat [ITT] analysis, p=0.149).[8] This may have been due to the study being underpowered. Ataluren increased the amount of dystrophin in muscle after treatment in this trial compared with placebo (significance not tested), [8] and also in the second non-randomised phase 2a trial (n=38) when compared versus pre-treatment levels.[9] However, the authors of the placebo-controlled phase 2b trial noted that their results were limited by the poor muscle biopsy sample quality which limited their ability to draw firm conclusions. The phase 2a study reported that changes in clinical measures such as timed function tests from baseline to 28 days were small and not significant, which was suggested to be due to the short period of treatment.

Drisapersen

Two RCTs[10, 12] assessed the use of drisapersen in boys with DMD who had confirmed deletions correctable by skipping exon 51. Treatment was initiated from age five[12] and seven[10] in these studies. Both studies considered renal events as adverse outcomes of special interest.

The first phase IIa study, used to evaluate dosage, including 21 boys identified a dose of 6mg/kg as the maximum tolerated dose.[10] Boys with existing renal disease were excluded and one case of renal toxicity was observed in the 9mg group. In the second phase II trial (n=53), continuous drisapersen (once weekly) significantly increased walking ability compared with placebo at week 25 (adjusted mean difference: 35.09 m, p=0.014). The difference between continuous drisapersen and placebo at 49 weeks was similar in magnitude, but did not quite reach significance (adjusted mean difference: 35.84 m, p=0.051). There was no difference in 6 minute walking distance (6MWD) changes from baseline between intermittent drisapersen (nine doses spread unevenly over a ten week cycle, see Appendix for details) and placebo at either timepoint. [12] Renal events occurred in all study groups with greater proportions for continuous and intermittent drisapersen.

Eteplirsen

In the RCT of eteplirsen (n=12), where boys began treatment from age nine, it increased the proportion of normal dystrophin-positive muscle fibres at week 24 compared with baseline ($p \leq 0.002$) while placebo-treated patients did not experience an increase (results pooled for 12 and 24 weeks). Even greater increases occurred with eteplirsen at week 48 ($p \leq 0.001$) suggesting that dystrophin increases with longer treatment.[11]

Boys receiving the 50 mg/kg/week dose of eteplirsen in this trial showed a significant improvement in ambulation (6MWD test) compared with placebo at 48 weeks ($p \leq 0.016$), but not those receiving the 30 mg/kg/week dose. This was reported to be due to rapid progression of disease in two patients in the 30 mg/kg/week group immediately after enrolment, and loss of ambulation at or after 24 weeks. If these two patients were excluded from the analysis, leaving

only the ambulation-evaluable patients treated with either dose of eteplirsen for 48 weeks, overall they experienced a 67.3 m benefit in the compared to placebo/delayed eteplirsen patients ($p \leq 0.001$).

The placebo/delayed eteplirsen patients switched over to either 30 or 50 mg/kg/week of eteplirsen after 24 weeks of placebo; this may reduce the apparent effect of eteplirsen at 48 weeks (although no significant effect on ambulation of either dose of eteplirsen was apparent at 24 weeks).

This study was very small, with just 12 boys, and the groups were not balanced at baseline (the 30 mg/kg/week eteplirsen group was older and had less walking ability on average), which may influence results. The analyses included baseline results and duration of DMD as covariates to try to take these differences into account, and additional analyses excluding the two outliers were also carried out.

Table 3: Summary of results of trials of disease modifying therapies

Study	Patients	Treatment groups	Mean age at treatment in years (SD), Range	Age of eligibility for study	Summary of key results	Current marketing authorisation
Ataluren						
Bushby 2014[8]	174 boys with DMD caused by a nonsense mutation. All three premature stop codons were represented.	Placebo 40mg/kg/day ataluren 80mg/kg/day ataluren	8.3 (2.33), 5 to 15 years 8.8 (2.91), 5 to 20 years 8.4 (2.53), 5 to 16 years	≥5 years	**Ambulation:** Ataluren 40 mg/kg/day - mean decline in 6MWD at 48 weeks:12.9m vs. 42.6m with placebo, difference: 29.7m; p=0.149, ITT analysis). **Dystrophin production:** Mean change in dystrophin/spectrin ratio at week 36: 2.8% with ataluren 40 mg/kg/day vs. 1.3% with ataluren 80 mg/kg/day vs. 0.09% with placebo (significance not tested; authors noted poor muscle biopsy quality)	In September 2014 Ataluren (Translarna™) was given 'conditional approval' by the European Medicines Agency (EMA) for the treatment of DMD caused by nonsense mutations in patients aged five years and older who are still walking. The conditional approval means that the company will need to provide the EMA with additional evidence on the effectiveness and safety of ataluren from an ongoing confirmatory study. The drug has orphan drug designation from the EMA, as well as the US Food and Drug Administration (FDA). Ataluren for DMD is currently being appraised as part of the National Institute for Health and Care Excellence (NICE) highly specialised technologies guidance programme, the guidance is expected to be published in February 2016.
Finkel 2013[9]	38 boys with nonsense mutation DMD	Ataluren: (1) 16mg/kg/day (2) 40mg/kg/day (3) 80mg/kg/day	8.3 (2.34), 5 to 11 years 8.5 (1.70), 6 to 12 years 9.6 (3.65), 5 to 17 years	≥5 years	**Dystrophin production:** % Mean change in dystrophin:spectrin ratio from baseline/% participants with positive change in ratio at 28 days: 16 mg/kg/day: 12.3% (p=0.13)/67% 40 mg/kg/day: 8.4% (p=0.09)/55% 80 mg/kg/day: 14.7% (p=0.15)/67% Overall (all doses pooled): 11% (p=0.008)/61%	

					Clinical measures: Changes in myometry measurements and timed function tests from baseline to 28 days reported as small and not significant (figures not provided).	
Drisapersen						
Flanigan 2014[10]	21 non-ambulant boys in wheelchair for ≥1 year but ≤4 years, and with a DMD mutation correctable by drisapersen	Single dose of: Placebo (matched to individual doses) 3 mg/kg drisapersen 6 mg/kg drisapersen 9 mg/kg drisapersen	12.2 years (0.84), 11 to 13 years 13.8 (1.72), 12 to 16 years 13.3 (1.21), 12 to 15 years 10.3 (1.53), 9 to 12 years	≥9 years	**Tolerability:** Doses of 3 and 6mg/kg were well tolerated but 9mg/kg resulted in acute inflammatory response and did not offer an increase in exposure compared to the 6mg/kg dose, the 12mg/kg dose was not investigated further as a result. Single doses of drisapersen at 3 and 6 mg/kg did not result in significant safety or tolerability concerns; however, at the 9 mg/kg dose, pyrexia and transient elevations in inflammatory parameters were seen. One case of renal toxicity occurred in the 9mg group. The maximum tolerated dose of 6 mg/kg drisapersen was identified	Drisapersen also has orphan drug status in the US and Europe. In June 2015 applications were reported to have been submitted to the EMA for Marketing Authorisation and to the FDA for a New Drug application. Drisapersen received rare Pediatric Disease Designation from the FDA in August 2015.
Voit 2014[12]	53 boys with drisapersen correctable DMD mutation in the DMD gene, could rise from the floor lying unaided ≤7s, had a	Placebo Continuous 6mg/kg drispersen Intermittent 6mg/kg drispersen	6.9 (1.2), NR 7.2 (1.7), NR 7.7 (1.5), NR	≥ 5 years	**Ambulation:** Week 25 (primary outcome): Continuous drisapersen significantly increased mean 6MWD compared with placebo (adjusted mean change from baseline: +31.5 m with drisapersen vs. -3.6 m with placebo, mean difference: 35.09 m, p=0.014). Week 49 (secondary outcome): Continuous drisapersen increased mean 6MWD compared with placebo but the difference was no longer significant (adjusted mean	

	6MWD of ≥75 m				change from baseline: +11.2 m with drisapersen vs. -24.7 m with placebo; adjusted mean difference: 35.84 m, p=0.0051). There was no significant difference in 6MWD change from baseline between intermittent drisapersen and placebo at either timepoint. Renal events were present in all groups (13 for continuous, 12 for intermittent and seven for placebo), most of which were subclinical proteinuria.	
Eteplirsen						
Mendell 2013[11]	12 boys with confirmed out-of-frame DMD deletions potentially correctable by eteplirsen; able to walk 200 to 400 m on the 6MWT	Placebo/delayed eteplirsen (after 24 weeks) 30 mg/kg/wk eteplirsen 50 mg/kg/wk eteplirsen [ambulation evaluable subgroup pooled across doses, n=6]	8.5 (1.7), 7 to 10 years 9.3 (0.50), 9 to 10 years 8.5 (1.3), 7 to 10 years [9.5 (0.71), 9 to 10 years]	7 to 13	**Dystrophin production:** There was no significant increase in the percentage of dystrophin-positive fibres with 50 mg/kg eteplirsen at week 12. However, at week 24 the percentage of dystrophin-positive fibres with 30 mg/kg eteplirsen was increased to 23% of normal (i.e. what would be expected in a person without DMD) (p≤0.002). There were no increases detected in placebo-treated patients (results pooled for 12 and 24 week biopsies). Even greater increases occurred at week 48 with ataluren (52% and 43% in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. **Ambulation:** Adjusted mean change in 6MWD from baseline to: 24 weeks (SD): -25.8 m (30.6) with placebo vs. -128.2 m (31.6) with 30 mg/kg eteplirsen and -0.3 m (31.2) with 50 mg/kg eteplirsen (difference between groups not significant).	A New Drug Application has been completed to the US FDA for eteplirsen but the outcome is not yet known.

					48 weeks (SD): -68.4 m (37.6) with placebo/delayed eteplirsen vs. -153.4 m (38.7) with 30 mg/kg eteplirsen (not significant vs. placebo) and +21 m (38.2) with 50 mg/kg eteplirsen (vs. placebo p≤0.016). The large decline in the 30 mg/kg group was due to 2 outliers who rapidly deteriorated immediately after enrolment and lost ambulation at or after 24 weeks. Excluding these 2 participants and including only ambulation-evaluable eteplirsen-treated patients receiving either eteplirsen dose (n=6), found that they experienced a 67.3 m benefit from baseline at week 48 compared to placebo/delayed eteplirsen patients (n=4, p≤0.001).	

Non-disease modifying therapies

Twelve studies reported on non-disease modifying therapies. Four studies[13-16] were identified that provided information on the effectiveness of treatment with corticosteroids at slowing the decline in muscle strength and function. Five studies[17-21] provided information on the effectiveness of other drug treatments at slowing the decline in muscle strength/function and cardiomyopathy and a further three studies[22-24] described non drug therapies. These studies are summarised in Appendix 9.

A randomised study investigated daily steroid dosing compared to weekend only and found broadly comparable outcomes, with reduced side effects.[13] Another study found that boys treated with steroids had a higher IQ than those given placebo when assessed at follow up. [16] Additionally, weight gain, which is a problem for boys with DMD receiving steroid treatment, was assessed for two different forms of steroids and found that deflazacort caused lower weight gains than prednisone.[14]

ACE inhibitors were found to be effective in slowing the progression of cardiomyopathy. One study compared ACE inhibitors to angiotensin blockers which were equally effective. [17] Sildenafil was found ineffective in improving cardiomyopathy, with high numbers of treated patients experiencing a ≥10% increase in Left Ventricular End-Systolic Volume (LVESV). [19] Idebenone was not found to have a significant difference when compared to placebo for reducing cardiorespiratory failure.[21] Some new therapies which have been studied since the last update are the addition of epleronone [20] and pentoxifylline.[18] At least six months of Eplerenone treatment reduced cardiac decline compared to placebo, whilst pentoxyfylline did not appear to offer much improvement.

Among the studies of non-drug therapies, supplementation with L-carnitine was found to be ineffective in improving function in patients not undergoing steroid treatment. [22]Assisted bicycle training was compared to no treatment with no significant differences observed for the six minute cycling test. [23] For treatment of scoliosis, surgical treatment improved spinal curvature outcomes compared with non-surgical treatment. [24]

<u>Discussion</u>

Overall there was a small amount of evidence regarding treatments which seek to alleviate the underlying genetic defect causing DMD or significantly improve symptoms or function.

Five[8-12] included studies that reported potentially disease modifying therapy were randomised but had small sample sizes ranging from 12 to 174. Ataluren treatment in boys with DMD caused by nonsense mutations reduced mean decline in walking distance compared with placebo, but this difference did not reach statistical significance. This– may have been due to a lack of statistical power, despite this trial being the largest of those assessing the potentially disease modifying therapies (n=174).

Drisapersen administered weekly provided increased 6MWD and this difference was statistically significant at 25 weeks but not 49 weeks. Eteplirsen, an exon 51 skipping genetic treatment, was found to significantly increase the number of normal dystrophin-positive fibres, providing an ambulation benefit after 48 weeks to patients treated with a dose of 50 mg/kg per week compared with placebo. The small number and size of the trials, and lack of statistically significant improvements in ambulation in most cases limits our ability to draw firm conclusions

on the effectiveness of these treatments. The treatments these trials have tested are estimated to only be appropriate for about 26% of boys with DMD.

All of these trials were in boys aged five and over, therefore the relevance of these treatments to screen detected DMD infants without clinical symptoms are not currently known. The development of ataluren is the most advanced of the three drugs, as it has been given conditional approval from the EMA. This approval is for boys aged five and over, therefore its license does not extend to use in younger boys and would not provide a benefit to those detected following newborn screening.

No studies were identified which suggested that steroids should be superseded as the primary form of treatment for DMD. Studies of non-disease modifying treatments indicated some benefit in the form of corticosteroids, exercise and surgical therapies, with all of these already recommended to boys with DMD. Novel therapies and treatments aiming to reduce cardiovascular complications were not found to be effective.

All of the trials were in males aged four to 38, therefore none of the treatments were started in the newborn period when screen detected boys would be identified. None of the trials assessed the impact of age at initiation of treatment on outcomes.

There had been no systematic reviews since the last update.

2b) Is there evidence that treatment following newborn screen adds any additional benefit in comparison with existing treatment pathways?

None of the studies identified explicitly assessed participants detected through newborn screening, or compared the effects of treatment in screen detected versus clinically detected boys or treatment given at different ages. Participants included in the studies ranged from 4 to 38 years where reported, i.e., treatments were not initiated in the newborn period, which is when those identified by screening would potentially be able to start treatment if appropriate.

Discussion

There was no new evidence about the impact of treatment following newborn screening in comparison with existing detection and treatment pathways.

Summary: Criterion 10 not met.

Genetic treatments that restore the normal reading frame of the DMD gene by reading through nonsense mutations or skipping of exon 51 affected by the mutation have shown the ability to slow decline in muscle deterioration. Such therapies have provided promising results and are in the approval stage. Genetic treatments may provide further improvements to the care of DMD patients. These treatments have thusfar only been tested in boys aged 5 years and older, which is the age at which clinical diagnosis occurs. They have not yet been tested at earlier ages when boys identified by newborn screening could potentially start treatment.

No studies were identified which assessed the impact of treatment following newborn screening in comparison with existing detection and treatment pathways. The identified studies provided

no direct assessment of potential treatment benefits following screening as none described participants as being detected through screening.

Additional research regarding effectiveness following early detection is needed to provide evidence to support a population based newborn screening programme. In order to establish the effectiveness of treatment following a screening programme, randomised controlled trials or prospective cohort studies are required to compare the outcomes in treated screen detected (or potentially siblings diagnosed in infancy after a proband is diagnosed) vs. clinically detected populations.

13b. Where screening is aimed solely at providing information to allow the person being screened to make an "informed choice" (eg. Down's syndrome, cystic fibrosis carrier screening), there must be evidence from high quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

Newborn screening aims to identify boys with raised CK levels at risk of being affected by DMD, and testing would need to be accepted by the parents. Screening and subsequent genetic testing to confirm results can facilitate the parents making an "informed choice" regarding their subsequent reproduction. The last review suggested some evidence that, despite the availability of information regarding the test, this may not be fully understood by the women who receive it. In particular, they may not fully understand that the test is optional, and the full implications of having the test. These include: reducing the diagnostic odyssey, improving timeliness of interventions, forward planning and allowing reproductive choices but also possible harms to healthy babies as a result of false positive results, changes to the child's early life experience and the possibility of side effect from early treatment. These issues would need to be addressed by a screening programme.

The previous NSC report suggested that parents' reproductive behaviour may not be largely influenced by the results of newborn screening.

Current UKNSC key question

3) Has any evidence been published since the last review that demonstrates wider effects/benefits from screening for DMD, such as on reproductive choices?

For this question systematic reviews and comparative studies were prioritised for inclusion.

Description of the evidence

No systematic reviews or comparative studies were identified which assessed whether screening had wider benefits, such as allowing the newborn's parents to make informed reproductive choices. However, two studies, a survey [25] and a mixed methods study [26 27] were identified that discussed parental attitudes. The survey found that parents of children with DMD and expectant parents were strongly in support of newborn screening for DMD.[25] The mixed methods study of parents whose child was clinically diagnosed, found it was preferred that screening took place in infancy (6-36 months) rather than newborn as parents felt the later diagnosis would have a lesser impact on parent-child relationships and that signs of DMD may be beginning to appear at

this time.[26] The later publication found that a delay in diagnosis has a negative impact on parents and put families at risk of having a subsequent affected child.[27] Half the survey respondents felt that their child could have been diagnosed earlier.

Summary: Criterion 13b not met

No new evidence was identified that assessed the wider effects of screening for DMD on the reproductive or other choices of the parents.

Conclusion

Implications for policy

This report assesses newborn screening for Duchenne muscular dystrophy (DMD) against select UK National Screening Committee (UK NSC) criteria for appraising the viability, effectiveness and appropriateness of a screening programme.

This review assessed key questions to determine if evidence published since 2011 suggests that the current recommendation on newborn screening of DMD in the UK should be reconsidered.

No direct evidence of clinical validity of a new high throughput screening test (i.e. not the standard approach based on total CK level testing on dried blood spot) or the additional benefits of early treatment following screening were identified. There is UK evidence of inadequate performance of total CK screening on newborn dried blood spot as a marker for screening for DMD

In order to establish the additional benefit of early treatment opportunities presented by screen detection, sufficiently large studies that assess variation in outcomes according to age of treatment initiation, with analyses using screening relevant age cutoffs (i.e. newborns or infants), are necessary.

The volume, quality and direction of evidence published since 2011 does not indicate that newborn screening for Duchenne muscular dystrophy should be reconsidered in the UK. Several uncertainties remain across key criteria, including:

- Lack of evidence regarding a reliable, high throughput screening strategy.
- Lack of evidence of additional benefit of early treatment following screen detection or an optimum age for treatment initiation which is dependent on screen detection.

Methodology

The draft update report was prepared by Bazian Ltd., and then adapted in discussion with the National Screening Committee. Each criterion was summarised as 'met', 'not met' or 'uncertain' by considering the results of the included studies in light of the volume, quality and consistency of the body of evidence. Several factors were assessed to determine the quality of the identified evidence, including study design and methodology, risk of bias, directness and applicability of the evidence. Factors that were determined to be pertinent to the quality of the body of evidence identified for each criterion are outlined in the results section as well as the comment section of the Appendix tables.

For Criterion 5, quality assessment focused on four main domains: patient selection, the index test, the reference standard, and flow and timing of index test and reference standard. Each domain was assessed for risk of bias, and the first three domains were assessed for applicability to a potential UK screening programme population. Details of these assessments can be found in the comment section of the Appendix tables.

Search strategy

EMBASE.com

1. 'duchenne muscular dystrophy':de
2. 'DMD':ti,ab
3. 'Duchenne muscular dystrophy':ti,ab
4. #1 or #2 or #3
5. 'newborn'/exp
6. neonat*:ti,ab
7. newborn*:ti,ab
8. #5 or #6 or #7
9. 'mass screening':de
10. screen*3:ti,ab
11. detect*3:ti,ab
12. (test or tests or testing):ti,ab
13. #9 or #10 or #11 or #12
14. 'newborn screening':de
15. #4 and #8 and #13
16. #4 and #14
17. #15 or #16
18. 'prevalence':de
19. 'incidence':de
20. (prevalen* or inciden*):ti,ab
21. 'epidemiological data':de
22. #18 or #19 or #20 or #21

23. 'predictive value'/exp
24. 'sensitivity and specificity':de
25. positive:ab,ti OR negative:ab,ti AND adj:ab,ti AND (predictive NEXT/1 value):ab,ti
26. 'false positive result':de or 'false negative result':de
27. (sensitiv* or specific*):ti,ab
28. #23 or #24 or #25 or #26 or #27
29. 'creatine kinase'/exp
30. ((CK or creatine kinase) and (assay or serum or elevated or level or blood)):ti,ab
31. #29 or #30
32. #28 and #31
33. (creatine NEXT/1 supplement*):ab,ti
34. 'corticosteroid'/exp
35. 'prednisone'/exp
36. 'prednisolone'/exp
37. (prednisone or prednisolone or deflazacort):ti,ab
38. ((experimental or novel) NEAR/3 (therap* or treatment*)):ti,ab
39. ‘antisense oligonucleotide*’:ti,ab
40. ‘exon skipping’:ti,ab
41. (AVI-4658 or eteplirsen or PRO051 or GSK2402968 or Drisapersen):ti,ab
42. (ataluren or PTC124):ti,ab
43. Gentamicin/
44. Gentamicin*:ti,ab
45. physiotherapy:ti,ab
46. #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45
47. ‘Anticipatory care’:ti,ab
48. ‘early diagnosis’:de
49. ‘delayed diagnosis’:de
50. 'disease course':de
51. ‘prognosis’:de
52. ‘quality of life’:de
53. ‘treatment outcome’/exp
54. ‘morbidity’:de
55. ‘mortality’:de

56. ‘reproductive behavior’:de

57. ‘genetic counselling’:de

58. 'parent':de

59. ‘decision making’/exp

60. ‘adaptive behavior’:de

61. ‘attitude to health’:de

62. #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61

63. #13 and #62

64. #22 or #32 or #46 or #63

65. #4 and #64

66. #17 or #65

67. #66 AND (2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py) AND [english]/lim AND [embase]/lim

PubMed

#68 Search (#17 OR #66) Filters: Publication date from 2011/01/01 to 2015/12/31 Sort by: PublicationDate 629

#67 Search (#17 OR #66) 2099

#66 Search (#4 AND #65) 1985

#65 Search (#22 OR #32 OR #46 OR #64) 3238674

#64 Search (#13 AND #63) 623323

#63 Search (#47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62) 2274155

#62 Search Attitude to health[MeSH Terms] 301037

#61 Search Health Knowledge, Attitudes, Practice[MeSH Terms] 74946

#60 Search Adaptation, psychological[MeSH Terms] 102815

#59 Search Decision making[MeSH Terms] 124790

#58 Search (parents[MeSH Terms]) AND psychology[MeSH Subheading] 38421

#57 Search genetic counseling[MeSH Terms] 11872

#56 Search Reproductive behavior[MeSH Terms] 6953

#55 Search Mortality[MeSH Terms] 286945

#54 Search Morbidity[MeSH Terms] 381182

#53 Search Treatment outcome[MeSH Terms] 679866

#52 Search "Quality of Life"[MeSH Terms] 122121

#51 Search Prognosis[MeSH Terms] 1131865

#50 Search Disease progression[MeSH Terms] 121066

#49 Search Delayed diagnosis[MeSH Terms] 2647

#48 Search Early diagnosis[MeSH Terms] 23143

#47 Search "Anticipatory care"[Text Word] 86

#46 Search (#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45) 225105

#45 Search physiotherapy[Text Word] 12551

#44 Search Gentamicin*[Text Word] 26280

#43 Search Gentamicins[MeSH Terms] 17189

#42 Search (ataluren[Text Word]) OR PTC124[Text Word] 108

#41 Search ((((AVI-4658[Text Word]) OR eteplirsen[Text Word]) OR PRO051[Text Word]) OR GSK2402968[Text Word]) OR Drisapersen[Text Word] 27

#40 Search exon skipping[Text Word] 1435

#39 Search antisense oligonucleotide*[Text Word] 15630

#38 Search ("experimental therap*"[Text Word] OR "experimental treatment*"[Text Word] OR "novel therap*"[Text Word] OR "novel treatment*"[Text Word]) 7451

#37 Search (prednisone[Text Word] OR prednisolone[Text Word] OR deflazacort[Text Word]) 82575

#36 Search (Prednisolone[MeSH Terms]) AND ("administration[MeSH Subheading] AND dosage"[MeSH Subheading] OR "adverse effects"[MeSH Subheading] OR "therapeutic use"[MeSH Subheading]) 37593

#35 Search (Prednisone[MeSH Terms]) AND ("administration[MeSH Subheading] AND dosage"[MeSH Subheading] OR "adverse effects"[MeSH Subheading] OR "therapeutic use"[MeSH Subheading]) 32194

#34 Search corticosteroid*[Text Word] 79697

#33 Search Creatine supplement*[Text Word] 686

#32 Search (#28 AND #31) 291944

#31 Search (#29 OR #30) 1485492

#30 Search ((assay[Text Word] OR serum[Text Word] OR elevated[Text Word] OR level[Text Word] OR blood[Text Word])) AND (CK[Text Word] OR "creatine kinase"[Text Word]) 26116

#29 Search (Creatine Kinase[MeSH Terms] AND analysis[Subheading] OR blood[Subheading]) 1477746

#28 Search (#23 OR #24 OR #25 OR #26 OR #27) 3567048

#27 Search (sensitiv*[Text Word]) OR specific*[Text Word] 3418843

#26 Search (false positive*[Text Word]) OR false negative*[Text Word] 77877

#25 Search ("positive predictive value*"[Text Word]) OR "negative predictive value*"[Text Word] 34425

#24 Search ("Sensitivity AND Specificity"[MeSH Terms]) 428559

#23 Search "Predictive Value of Tests"[MeSH Terms] 146861

#22 Search (#18 OR #19 OR #20 OR #21) 2550765

#21 Search Epidemiologic Studies[Mesh Terms] 1701627

#20 Search (prevalen* OR inciden*[Text Word]) 1187949

#19 Search Incidence[MeSH Terms] 180361

#18 Search Prevalence[MeSH Terms] 197158

#17 Search (#15 OR #16) 188

#16 Search (#4 AND #14) 37

#15 Search (#4 AND #8 AND #13) 188

#14 Search Neonatal Screening[MeSH Terms] 7429

#13 Search (#9 OR #10 OR #11 OR #12) 4646266

#12 Search (test OR tests OR testing[Text Word]) 3000793

#11 Search detect*[Text Word] 1732493

#10 Search screen*[Text Word] 548232

#9 Search Mass screening[MeSH Terms] 101662

#8 Search (#5 OR #6 OR #7) 700399

#7 Search newborn*[Text Word] 635553

#6 Search neonat*[Text Word] 223015

#5 Search Infant, Newborn[MeSH Terms] 500651

#4 Search (#1 or #2 or #3) 8985

#3 Search Duchenne muscular dystrophy[Text Word] 7660

#2 Search DMD[Text Word] 4871

#1 Search Muscular Dystrophy, Duchenne[MeSH Terms] 3352

Cochrane Library (Wiley)

#1 MeSH descriptor: [Muscular Dystrophy, Duchenne] explode all trees

#2 DMD:ti,ab

#3 "Duchenne muscular dystrophy":ti,ab

#4 #1 or #2 or #3

Appendices

Appendix number	1
Relevant criteria	5
Publication details	Moat et al. Newborn bloodspot screening for Duchenne Muscular Dystrophy: 21 years experience in Wales (UK). European Journal of Human Genetics. 21(10) 12049-1053
Study details	Welsh Screening Programme 1990 - 2011
Study objectives	To review screening programme experience to help inform future policy on newborn bloodspot screening for DMD.
Inclusions	Newborn male infants born in Wales. Participation was on a voluntary basis.
Exclusions	Female newborns
Population	343,170 newborn males who were screened
Intervention/test	Initial CK testing using a fluorimetric assay on newborn DBS, usually collected between five and eight days of birth. Those samples with CK levels above 200U/l were retested in duplicate. If mean of triplicate results was >250U/l then clinical appointment and referral were arranged. At the referral appointment a venous blood sample was collected for serum CK analysis, and also often a sample for possible genetic analysis. If CK levels were elevated (not further defined) further investigations (genotyping and muscle biopsy) were discussed with the parents.
Comparator	NA
Results/outcomes	CK screen positives: 145 (0.042%) Confirmed elevated CK: 66 (at 6-8 weeks) True positives: 56 False positives: 89 (includes 5 with BMD, and 5 other forms of muscular dystrophy) False positive rate: 0.023% False negatives: 13 (identified after clinical presentation) Sensitivity: 81.6%

	Specificity: 99.97% PPV: 38.6%

Comments

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Y	Low	All male newborns invited for participation.
Case-control design avoided?	Y	Low	Not a case control study.
Inappropriate exclusions avoided?	Y	Low	Exclusion of female newborns, which is appropriate given that DMD is X linked
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Low	Actual screening programme results, so "index test" performed before diagnostic test. Reference standard not carried out on all screened individuals.
Threshold pre-specified?	Y	Low	Thresholds for CK pre-specified. Derived from analysis of anonymised blood spots.
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Y	Low	DNA testing used for confirmation of diagnosis, which is likely to correctly classify the condition. However, DNA testing not carried out on screen negatives. False negatives were identified when they presented clinically; routine follow up of screen negatives was not reported. Given the long period covered clinical presentation would be expected for at least some of those who had been screened earlier in the programme. However for boys screened towards the end of the screening programme there may not have been time for symptoms to appear and diagnosis to have taken place.
Reference standard results interpreted	NA	NA	Pilot screening programme assessment, so only screen positives assessed by DNA

without knowledge of index test results?			testing.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	NA	NA	Pilot screening programme assessment
Did all participants receive same reference standard?	N	High	This was a pilot screening programme assessment and DMD status of screen negatives was not tested; not possible to determine if DMD positives identified represent all DMD patients from the screening sample.
All patients included in analysis?	N	High	This was a pilot screening programme assessment and DMD status of screen negatives was not tested. While a number of false negatives were identified through clinical presentation, routine follow up of screen negatives was not carried out, and completeness of ascertainment of DMD diagnoses among screen negatives was not clear.
Applicability			
Applicable to UK screening population of interest?	Y	Low	Newborn testing is age group of interest.
Applicable to UK screening test of interest?	Y	Low	Newborn blood spot testing is already carried out in the UK for other disorders, and DNA testing currently used for diagnosis in the UK, so should be generalizable. However this screening programme was ceased due to the programme being unable to obtain appropriate standards.
Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	Yes, DMD is the condition of interest.

Appendix number	2
Relevant criteria	5

Publication details	Mendell et al. Evidence-based path to newborn screening for duchenne muscular dystrophy. Annals of Neurology. 71(3): 304-313[6]
Study details	Pilot screening programme, Ohio, USA between 2007 and 2011.
Study objectives	To assess the performance of a 2-tiered method for DMD newborn screening (NBS) on dried blood spot (DBS), with initial screening for CK followed by DNA isolation and DMD gene analysis on the same dried blood spot. The use of DNA analysis on the same blood spot was aimed to suit the US system, where follow up of infants to retest venous blood several weeks after birth was reported to be impractical. In addition, it aimed to reduce the number of false positives that would be expected based on CK alone.
Inclusions	Newborn male infants born at any of the participating hospitals were eligible for the study. Participation was on a voluntary basis.
Exclusions	Female newborns
Population	37,649 newborn males contributed to assessment of test performance • Phase 1: n=30,547 consecutive anonymous newborn DBS initially used to identify population distribution of CK values • Phase 2: n=6,928 – initial pilot study (1 hospital) • Phase 3: n=10,937 - pilot rolled out to the State (43 hospitals). • Phase 4: n=19,884 anonymous newborn DBS samples obtained to expand sample size (also females, not reported here)
Intervention/test	Initial CK testing using a fluorimetric assay on newborn DBS, usually collected between 24 and 48 hours of birth. Those with CK levels above a specified threshold had DNA testing on the same dried blood spot. In phase 2 a CK threshold of ≥600U/l was used for DNA testing, this was raised to ≥ 750U/l subsequently. For CK results above the threshold for DNA testing but negative for DMD, a venous blood CK was requested through the boy's primary care physician. If any boy was identified as having raised CK at this stage the research staff offered to make an

	appointment for the boy at the nearest Muscular Dystrophy Association clinic for further testing.
Comparator	NA
Results/outcomes	**Phase 2 (CK threshold ≥600U/l)*:** CK screen positives: 110 True positives: 2 False positives: 108 False positive rate: 1.6% To further reduce false positives, the threshold was raised in phase 3 to ≥750U/l **Phase 3 (CK threshold ≥750U/l)*:** CK screen positives: 58 True positives: 1 False positives: 57 False positive rate: 0.52% * Values for creatine kinase test only versus DNA testing on blood spot as diagnostic reference standard **Retesting of venous CK in screen positives without DMD mutations:** 43 of the 165 false positives were retested for venous CK levels. In most cases follow up venous CK was lower than bloodspot derived. Highest non DMD CK was 1,700U/l, however, the venous blood showed a CK of 46 U/l. In two cases CK remained slightly elevated >500U/l. Whether these individuals were tested for DMD mutations or other causes of raised CK was not reported. **Phase 4 (CK threshold ≥750U/l):** CK screen positives: Unclear (308 reported but unclear if this was for phase 4 or overall) Other test performance characteristics: not reported **<u>Mutation analysis</u>** Overall DMD gene mutations (all exonic deletions) were found in 6 of 37,649 newborn males, all of whom had CK levels >

	2,000U/l. In 3 newborns with CK > 2,000U/l in whom DMD gene abnormalities were not found, limb-girdle muscular dystrophy gene mutations affecting DYSF, DYSF and FKRP were identified.

Comments

No systematic follow up to identify possible false negatives was reported, therefore they may be missed. The study reported a false positive rate

Question	Assessment (Y, N, unclear)	Risk of Bias (low, high, unclear)	Supporting info
Domain I: Patient selection			
Consecutive or random sample of population enrolled?	Unclear	Unclear	Does not report programme selection methods.
Case-control design avoided?	Y	Low	Not a case control study.
Inappropriate exclusions avoided?	Y	Low	Exclusion of female newborns, which is appropriate given that DMD is X linked
Domain II: Index Test			
Index test results interpreted without knowledge of reference standard results?	Y	Low	Pilot screening programme results, so "index test" performed before diagnostic test.
Threshold pre-specified?	Y	Low	Thresholds for CK pre-selected based on previous trial phase.
Domain II: Reference standard			
Reference standard likely to correctly classify condition?	Y	Low	DNA testing used for confirmation of diagnosis, which is likely to correctly classify the condition. However, DNA testing not carried out on screen negatives, so false negatives will not be identified.
Reference standard results interpreted without knowledge of index test results?	NA	NA	Pilot screening programme assessment, so only screen positives assessed by DNA testing.
Domain IV: Test strategy flow and timing			
Appropriate interval between index test and reference standard?	NA	NA	Pilot screening programme assessment

Did all participants receive same reference standard?	N	High	DMD status of screen negatives not tested; not possible to determine if six true positives represent all DMD patients from the screening sample.
All patients included in analysis?	N	High	Not possible to calculate specificity (Sp), sensitivity (Sn), PPV or NPV due to lack of data on screen negatives' true DMD status.
Applicability			
Applicable to UK screening population of interest?	Y	Low	Newborn testing is age group of interest.
Applicable to UK screening test of interest?	Y	Low	Newborn blood spot testing is already carried out in the UK for other disorders, and DNA testing currently used for diagnosis in the UK, so should be generalizable. CK screening for screening was ceased due to the programme being unable to obtain appropriate standards. The Welsh programme differed to the one in Ohio as three CK readings with a mean ≥ 250U/l would lead to a 6-8 week follow-up serum CK test and genotyping/muscle biopsy studies. In Ohio CK and DNA tests were carried out on the same blood spot.
Target condition measured by reference test applicable to UK screening condition of interest?	Y	Low	DMD

Appendix number	3
Relevant criteria	10
Publication details	Bushby et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. Muscle Nerve. 50(4):477-87. 2014[8]
Study details	Randomised, double blind, placebo controlled trial.
Study objectives	To evaluate the efficacy and safety of two doses of ataluren in patients with nonsense mutation DMD.
Inclusions	Male, ≥5 years of age with a documented nonsense mutation in the dystrophin gene, onset of dystrophinopathy symptoms by age 9 years, elevated serum

	creatine kinase (CK), and difficulty ambulating but able to walk ≥75 meters unassisted during a 6 minute walking test (6MWT) at screening for study entry. Stable use of concomitant glucocorticoids was allowed.
Exclusions	NR
Population	174 Boys with DMD caused by a nonsense mutation. All three premature stop codons were represented, it was not described whether boys were identified by screening. Age- Mean (SD) Range Placebo - 8.3 (2.33) 5 to 15 40mg/kg/day – 8.8 (2.91) 5 to 20 80mg/kg/day – 8.4 (2.53) 5 to 16
Intervention/test	Ataluren orally 3 times daily. Group one: 10, 10, and 20 mg/kg respectively during the day (i.e. last dose of the day was 20 mg/kg), totalling 40 mg/kg daily Group two:- 20, 20, 40 mg/kg respectively during the day, totalling 80 mg/kg daily
Comparator	Placebo
Results/outcomes	Ataluren 40 mg/kg/day reduced decline in walking ability after 48 weeks compared with placebo, but this difference did not reach statistical significance (mean decline in 6MWD: 12.9 m with ataluren 40 mg/kg/day vs. 42.6m with placebo, p=0.149). The higher dose of ataluren (80 mg/kg/day) showed little difference from placebo at week 48. Ataluren increased the amount of dystrophin in muscle after 36 weeks' treatment compared with placebo. Mean change in dystrophin/spectrin ratio: 2.8% with ataluren 40 mg/kg/day vs. 1.3% with ataluren 80 mg/kg/day vs. 0.09% with placebo (significance not tested).
Comments This was a randomised double blind study assessing the use of ataluren. Analysis was performed using the intention to treat principle. This study did not report a power calculation, and low power was suggested by the authors as potentially being responsible for the lack of significant findings. The authors noted that the muscle biopsies were of poor quality so this compromised their ability to interpret the dystrophin findings.	

Appendix number	4
Relevant criteria	10
Publication details	Finkel et al. Phase 2a study of ataluren-mediated dystrophin production in patients with nonsense mutation Duchenne muscular dystrophy. PLoS ONE. 8 (12)2013.[9]
Study details	Open-label, sequential dose-ranging study (non randomised, phase 2a)
Study objectives	To evaluate pharmaco-dynamic activity of an increase in dystrophin production on muscle biopsy.
Inclusions	Inclusion Criteria Patients who met all of the following conditions were eligible for enrolment into the study: 1. Diagnosis of DMD based on a clinical phenotype that had presented by 5 years of age, with increased serum CK levels and diminished staining for dystrophin on a muscle biopsy. 2. Presence of a nonsense mutation in the dystrophin gene. 3. Documentation that dystrophin gene sequencing had been performed by the University of Utah (Salt Lake City, Utah, USA) or, if sequencing had not previously been performed by the University of Utah, that a blood sample had been sent to the University of Utah for the confirmatory dystrophin gene sequencing. 4. Physical examination or radiographic imaging evidence of extensor digitorum brevis (EDB) muscles in both feet. 5. Ability to ambulate or, if nonambulatory, no requirement for ventilator support. 6. Male sex. 7. Age ≥5 years. 8. If known to be sexually active, willingness to abstain from sexual intercourse or to employ a barrier or medical method of contraception during the trial. 9. Willingness and ability to comply with the study requirements. 10. Ability to provide written informed consent if ≥18 years of age or written informed assent (with parental/guardian consent) if ≥7 years of age but <18 years. Consent of the parent or legal guardian alone was obtained for patients who were

	<7 years of age. 11. Documentation of a personally signed and dated informed consent document (assent was also required for children ≥7 years but <18 years of age) indicating that the patient, parent, or legal guardian had been informed of all pertinent aspects of the trial.
Exclusions	1. Prior or ongoing medical condition (eg, concomitant illness, psychiatric condition, alcoholism, drug abuse), medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator's opinion, could have adversely affected the safety of the patient, made it unlikely that the course of treatment or follow-up would be completed, or impaired the assessment of study results. 2. Clinical symptoms and signs of congestive cardiac failure (American College of Cardiology/American Heart Association Stage C or Stage D [1]). 3. Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test. 4. Hemoglobin <10 g/dL. 5. Serum albumin <2.5 g/dL. 6. Abnormal gamma-glutamyl transferase (GGT) or total bilirubin (above upper limit of normal [ULN] based on the laboratory's reference range). 7. Abnormal renal function (serum creatinine >1.5 times the ULN based on the laboratory's reference range). 8. History of solid organ or hematological transplantation. 9. Ongoing immunosuppressive therapy with agents other than corticosteroids. 10. Exposure to another investigational drug within 28 days before the start of study treatment. 11. Ongoing participation in any other therapeutic clinical trial at the time of enrollment in this study. 12. Ongoing use of thiazolidinedione peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists, eg, rosiglitazone (Avandia or equivalent) or pioglitazone (Actos or equivalent). 13. Change in systemic corticosteroid therapy (eg, initiation of treatment; cessation of treatment; or change in dose, schedule, or type of steroid) within 3 months before the start of study treatment. 14. Treatment with systemic aminoglycoside antibiotics within 4 weeks before the start of study treatment. Patients were allowed to receive systemic

	antibiotics as clinically necessary for life-threatening infections during the study; however, use of aminoglycoside antibiotics was to be avoided if possible.
Population	38 boys with nonsense mutation DMD Age- Mean (SD) Range Group one (16 mg/kg/day) 8.3 (2.34), 5 to 11 years Group two (40 mg/kg/day) 8.5 (1.70), 6 to 12 years Group three (80 mg/kg/day) 9.6 (3.65), 5 to 17 years
Intervention/test	Ataluren oral suspension three times per day at morning, midday, and evening. Doses: Group one - 4, 4, and 8 mg/kg, i.e. total 16 mg/kg/day Group two - 10, 10, 20 mg/kg, i.e. total 40 mg/kg/day Group three - 20, 20, 40 mg/kg, i.e. total 80 mg/kg/day
Comparator	n/a (dose comparison only)
Results/outcomes	Twenty three of 38 (61%) boys demonstrated increases in post-treatment dystrophin expression in a quantitative analysis assessing the ratio of dystrophin to spectrin after 28 days. A qualitative analysis also showed positive changes in dystrophin expression, with at least 2 of 3 reviewers observing increases in staining for dystrophin. Overall 2/6 in the 16mg/kg/day, 8/20 for 40mg/kg/day and 3/12 in the 80 mg/kg/day group. Quantitative findings were a mean change overall (across all doses) from pre to post treatment of 11% (p=0.008) of dystrophin expression. Mean % change/proportion positive(%) from pretreatment in dystrophin:spectrin ratio: 16 mg/kg/day – 12.3 (p=0.13)/67% 40 mg/kg/day – 8.4 (p=0.09)/55% 80 mg/kg/day - 14.7 (p=0.15)/67% Response did not appear dependant on age, corticosteroid use, or location or type of nonsense mutation in either method. Changes to clinical measures, upper and/or lower extremity scores and timed function tests (such as standing from supine, running 10 m, and climbing 4 standard stairs) were small and not statistically significant after 28 days of ataluren treatment (figures not provided). Adverse events were mild to moderate with procedural complications (78%) being

	the most common, followed by gastrointestinal events (57.9%).
Comments The groups were not randomised. All boys included completed the study and were analysed. A higher range of ages and weights were found in the 80mg/kg group due to the inclusion of a number of older non ambulatory boys. The study did not provide details of clinical outcomes, therefore it is difficult to fully assess the functional impact of the changes in dystrophin production seen. Changes in these outcomes were reported to be small and not statistically significant. This was suggested to be due to the short treatment period (28 days), which was much shorter than other trials of the potentially disease modifying treatments which lasted 24 to 48 weeks.	

Appendix number	5
Relevant criteria	10
Publication details	Flanigan et al. Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial. Neuromuscular Disorders. 24(1): 16-24. 2014. [10]
Study details	Double-blind randomised controlled trial
Study objectives	To assess was to assess the safety, tolerability, and pharmacokinetics of drisapersen after a single subcutaneous administration at different dose levels in non-ambulant subjects with DMD.
Inclusions	Non-ambulant boys aged ≥9 years, in wheelchair for at least one year but no more than 4 years, and with a diagnosis of DMD resulting from a mutation correctable by treatment with drisapersen
Exclusions	Mutations not correctable by drisapersen, a history of renal or hepatic disease, or with symptomatic cardiomyopathy.
Population	21 boys were assessed for eligibility, of whom 20 were randomised into the study at 2 study sites, one in the US (n = 16), and one in France (n = 4). Mean age (SD) range: Placebo - 12.2 years (0.84) 11 to 13 years; 3 mg/kg Drisapersen - 13.8 (1.72) 12 to 16 years; 6 mg/kg Drisapersen - 13.3 (1.21) 12 to 15 years; 9 mg/kg Drisapersen - 10.3 (1.53) 9 to 12 years
Intervention/test	Group one: 3 mg/kg drisapersen (n=6) or placebo (n=2); Group two: 6 mg/kg drisapersen (n=6) or placebo (n=2); Group three: 9 mg/kg drisapersen (n=3) or placebo (n=1);

	Group four: 12 mg/kg drisapersen or placebo – this group was planned but not carried out, as results suggested the 9 mg/kg dose was above the maximum tolerated dose
Comparator	Dose matched placebo
Results/outcomes	Each dose was investigated sequentially and this study was the first to investigate doses above 6mg/kg in DMD patients. Doses of 3 and 6mg/kg were well tolerated but 9mg/kg resulted in acute inflammatory response and did not offer an increase in exposure compared to the 6mg/kg dose, the 12mg/kg dose was not investigated further as a result. Dose proportionality, measured by Cmax and AUC, was not demonstrated over the 3–9 mg/kg dose range, this was more feasible over the 3–6 mg/kg range. Single doses of drisapersen at 3 and 6 mg/kg did not result in significant safety or tolerability concerns; however, at the 9 mg/kg dose, renal toxicity, pyrexia and transient elevations in inflammatory parameters were seen. The maximum tolerated dose of 6 mg/kg drisapersen was identified for further characterisation in multiple dose studies in the non-ambulant DMD population.
Comments This is a small study where boys were randomly assigned to treatment groups. This study aimed to establish the maximum tolerated dose for further study, it did not assess the impact of drisapersen on clinical outcomes. No major differences between treatment groups except 6mg/kg drisapersen were heavier than the other treatment groups and the 9mg/kg group were younger on average than the other treatment groups. The 9mg/kg group also had a shorter time since first symptoms, diagnosis and loss of ambulation.	

Appendix number	6
Relevant criteria	10
Publication details	Voit et al. Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study 2014. Lancet Neurology 2014; 13:987-96[12]
Study details	Randomised controlled trial (Australia, Belgium, France, Germany, Israel, Netherlands, Spain, Turkey, UK)
Study objectives	To investigate the safety and efficacy of drisapersen
Inclusions	Male patients were eligible if they were aged 5 years or older, had DMD and a confirmed drisapersen correctable mutation in the DMD gene, could rise from the

<table>
<tr><td></td><td>floor lying unaided in 7s or less, had a 6 min walking distance (6MWD) of 75 metres or more, had a 6MWD and rise from floor assessments of 20% of each other at the two screening visits (later amended to require only 6MWD assessments to be made within 20% of each other at the two screenings). Another inclusion criterion was glucocorticosteroid treatment for 6 or more months (stable dose and regimen for ≥3 months before screening and for the duration of the study).</td></tr>
<tr><td>Exclusions</td><td>No additional exclusions.</td></tr>
<tr><td>Population</td><td>53 patients were recruited and completed the study. Mean age for the total study population was 7.3 years (SD 1.5; range 5-11)

Mean age (SD) range by group: placebo 6.9 (1.2), not reported (NR); continuous drisapersen 7.2 (1.7), NR; intermittent drisapersen 7.7 (1.5), NR</td></tr>
<tr><td>Intervention</td><td>Drispersen 6mg/kg subcutaneous injections - continuous or intermittent regimen

Both groups: 3 weeks at loading dose (twice weekly doses)

Continuous: Once weekly dose after loading period

Intermittent: After loading period, 9 doses given over a 10 week cycle: twice weekly dose in weeks 1, 3 and 5, once weekly dose in weeks 2, 4, and 6, no injections in weeks 7-10</td></tr>
<tr><td>Comparator</td><td>Placebo</td></tr>
<tr><td>Results/outcomes</td><td>At week 25, continuous drisapersen increased mean 6MWD by 31.5m from baseline with a mean difference from baseline of 35.09m versus placebo. There was no significant difference in 6MWD change from baseline between intermittent drisapersen and placebo. Common adverse events were injection site reactions (14 patients given continuous drisapersen, 15 patients given intermittent drisapersen and six given placebo), renal events (13 for continuous, 12 for intermittent and seven for placebo), most of which were subclinical proteinuria. None of the serious adverse events reported (one for continuous, two for intermittent and two for placebo) resulted in withdrawal from the study.

<table>
<tr><td></td><td>Placebo</td><td>Drisapersen 6mg/kg continuous</td><td>Drisapersen 6mg/kg intermittent</td></tr>
<tr><td>Baseline</td><td></td><td></td><td></td></tr>
<tr><td>Number of patients</td><td>18</td><td>18</td><td>17</td></tr>
<tr><td>Mean 6MWD (SD)</td><td>403.18 (45.13)</td><td>427.61 (70.05)</td><td>394.57 (66.95)</td></tr>
<tr><td>Week 25 (primary endpoint)</td><td></td><td></td><td></td></tr>
<tr><td>Number of patients</td><td>16</td><td>16</td><td>15</td></tr>
</table>
</td></tr>
</table>

	Adjusted mean change (SE)	-3.6 (9.7)	+31.5 (9.8)	-0.1 (10.3)
	Adjusted mean difference vs placebo (95% CI)		+35.09 (+7.59 to +62.60)	+3.51 (-24.34 to +31.35)
	P value		0.014	0.801
	Week 49 (secondary endpoint)			
	Number of patients	17	18	15
	Adjusted mean change (SE)	-24.7 (12.8)	11.2 (12.6)	2.4 (13.6)
	Adjusted mean difference vs placebo (95% CI)		+35.84 (-0.11 to +71.78)	27.08 (-9.83 to +63.99)
	P value		0.051	0.147

Comments

This randomised controlled trial assessed the efficacy of two drisapersen regimens at 25 weeks. Analyses were assessed using the intention to treat principle.

The intermittent drisapersen group had a higher number of children over seven years (59%) compared with 28% in the placebo group and 39% in the continuous group. The intermittent group were also taller, heavier and had a longer period of time since diagnosis and first corticosteroid use.

Appendix number	7
Relevant criteria	10
Publication details	Mendell et al. Eteplirsen for the treatment of Duchenne Muscular Dystrophy. Annals of Neurology 2013. 74:637-647.[11]
Study details	Randomised controlled trial
Study objectives	To test eteplirsen's ability to induce dystrophin production and improve distance walked.
Inclusions	Boys aged 7 to 13 years with confirmed out-of-frame DMD deletions potentially correctable by skipping exon 51 and the ability to walk 200 to 400 m on the 6MWT were eligible for this study. Patients had to have been on stable glucocorticoids (prednisone or deflazacort) for 24 weeks to be enrolled, including: 8 DMD boys taking 18–25 mg/day deflazacort; 1 boy on 20 mg/day prednisone, and another 2 boys taking 25 mg/day prednisone. One boy was taking a prednisone weekend dosing regimen of 75 mg on Fridays and 75 mg on

	Saturdays. Cardiac and pulmonary functions were stable.
Exclusions	No additional exclusions.
Population	12 boys with DMD with 5 different genotypes resulting in out-of-frame deletions correctable by exon 51 skipping. Mean baseline 6MWT distance for all participants was 381.9m (range 261 to 456). Patients in the 30 mg/kg cohort were older, taller, and heavier than the other 2 cohorts. The mean distance walked by the 30 mg/kg cohort at baseline was approximately 40 m less than that of the 2 other cohorts. The authors reported that mean distances on the 6MWT at baseline were similar to those in other DMD studies. Mean age(SD) by group Placebo 8.5 (1.7), 7 to 10 years 30mg/kg/wk eteplirsen 9.3 (0.50), 9 to 10 years 50mg/kg/wk eteplirsen 8.5 (1.3), 7 to 10 years Ambulation evaluable subgroup pooled across doses 9.5 (0.71), 9 to 10 years
Intervention/test	Two dosing regimens of eteplirsen, 30 mg/kg/wk or 50 mg/kg/wk were administered by infusion
Comparator	Placebo. Patients receiving placebo were crossed over to weekly dosing with Eteplirsen of either 30 or 50mg/kg from week 25. Referred to as Placebo/delayed after this point.

<table>
<tr><td>Results/outcomes</td><td>Mean change from baseline (BL) in the percentage of dystrophin-positive muscle fibres by treatment group, p values are for comparison between Eteplirsen and placebo using the combined results from weeks 12 and 24:

<table>
<tr><td></td><td>Week 12 Mean change from BL, SE (p value)</td><td>Week 24 Mean change from BL SE (p value)</td><td>Week 48 Mean change from BL, SE (p value)</td></tr>
<tr><td>All Eteplirsen (n=8)</td><td>NA</td><td>NA</td><td>47.3, 3.89 (≤0.001)</td></tr>
<tr><td>Eteplirsen 30mg/kg (n=4)</td><td>NR</td><td>22.9, 2.90 (≤0.002)</td><td>51.7, 3.54 (≤0.001)</td></tr>
<tr><td>Eteplirsen 50mg/kg (n=4)</td><td>0.8, 3.55 (NS)</td><td>ND</td><td>42.9,6.72 (≤0.008)</td></tr>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td>Placebo/Delayed eteplirsen (n=4)</td><td>-4.0, 2.92</td><td>-4.0,2.92</td><td>37.7, 6.30 (≤0.009)</td></tr>
<tr><td>Eteplirsen 30mg/kg (n=2)</td><td>ND</td><td>-7.48, 1.00</td><td>33.6, 5.23</td></tr>
<tr><td>Eteplirsen 50mg/kg (n=2)</td><td>-0.6, 5.16</td><td>ND</td><td>41.8, 13.30</td></tr>
</table>
BL baseline, NA not applicable, ND not done, NS not significant, SE standard error

At week 24, the 30 mg/kg eteplirsen patients were biopsied, and percentage of dystrophin-positive fibres was increased to 23% of normal (i.e. what would be expected in a person without DMD); no increases were detected in placebo-treated patients (p=.002). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts, respectively), suggesting that dystrophin increases with longer treatment. Restoration of functional dystrophin was confirmed by detection of the restoration of components of the dystrophin-associated protein complex (e.g. sarcoglycans).

Ambulation:

Adjusted mean change in 6MWD from baseline to 24 weeks (SD): -25.8 m (30.6) with placebo vs. -128.2 m (31.6) with 30 mg/kg eteplirsen and -0.3 m (31.2) with 50 mg/kg eteplirsen (difference between groups not significant). The large change in the 30 mg/kg cohort was due to a rapid disease progression in 2 participants immediately after enrolment (these participants were the tallest and among the oldest in the trial, and had the lowest baseline 6MWD values). Excluding these two participants gave the 30 mg/kg group a change from baseline of 14.2 m</td></tr>
</table>

	(14.4). Adjusted mean change in 6MWD from baseline to 48 weeks (SD): -68.4 m (37.6) with placebo/delayed eteplirsen vs. -153.4m (38.7) with 30 mg/kg eteplirsen (not significant vs. placebo) and +21 m (38.2) with 50 mg/kg eteplirsen (vs. placebo p≤0.016). The large change in the 30 mg/kg cohort was again due to the 2 participants with rapid disease progression. Excluding these two participants gave the 30 mg/kg group a change from baseline of 31.5 m (19.9). Analysing only the ambulation-evaluable eteplirsen-treated patients receiving either Eteplirsen dose (i.e. excluding the two outliers), showed that they experienced a 67.3 m benefit from baseline at week 48 compared to placebo/delayed eteplirsen patients (p≤0.001).
Comments This study was very small, and may not be representative of what would be seen in a larger group. The groups were not balanced at baseline (potentially due to small sample size), and this may influence results. The group receiving 30 mg/kg were older, taller, and heavier than the other 2 groups and could walk about 40 m less far in the 6MWT. The analyses included baseline results and duration of DMD as covariates to try to take these differences into account. The ambulation analyses were also carried out excluding the two outliers who declined rapidly after enrolment and lost ambulation.	

Appendix 8: Summary of results of studies of non-disease modifying therapies					
Study	**Patients**	**Treatment**	**Age at treatment Mean (unless specified)**	**Age of eligibility for study**	**Summary of key results**
Corticosteroid Treatment					
Escolar 2011[13] RCT	64 ambulant, steroid-naïve boys	Weekend versus daily dosing of prednisone	7.3 years	4 – 10 years	QMT arm and leg scored were within the defined equivalence limits, as well as muscle strength outcomes for QMT elbow flexors and extensors. Timed tests for 10 meter walk, 4 step climb and supine to stand were also equivalent. Equivalence was not met for the secondary muscle outcomes of MMT, QMT grip, and QMT knee tests. The side effect profiles were almost identical at 12 months with no significant differences in the assessments of anthropometrics, vital signs, DEXA, and CBCL. There was no significant difference in the primary safety endpoint, BMI at 12 months.
Karimzadeh 2012[14] RCT	34 boys, muscular weakness below the age of 5	Treatment with deflazacort or prednisone for a period of 18 months	NR	NR	After one year the percentage of weight increase in the deflazacort group was lower that the prednisone group, pointing to a higher increase in weight in the prednisone group. There were no other side effects reported for either drug.
Sato 2014[16] Non randomised comparative study	29 boys	Prednisone or no treatment	Treated group 5.9 years Control group 6.1 years	NR	After two years IQ level had increased significant in the treated group a mean increase of 4.4 points more than the untreated group. Those with a nonsense point mutation showed greater improvement than deletion or duplication mutations. Gluteus maximus strength differed significantly between the two groups. The control group saw a gradual increase in the time taken to stand up whilst the treated group stayed roughly the same. At two years there was no significant difference in iliopsoas strength.

Cardiovascular treatment					
Allen 2013[17] RCT	22 boys	Lisonopril (Angiotensin converting enzyme inhibitor) Losartan (angiotensin II receptor blocker)	12.5 years - lisinopril 15.5 years – losartan (Median)	Any age	This study found no therapeutic difference between the two drugs from a one year follow up, suggesting that they are equally effective at treating cardiomyopathy of DMD
Leung 2014[19] RCT	20 DMD with cardiomyopathy	Sidenafil or placebo	Treated 25.5 years Placebo 22.6 years	≥ 18 years	Trial was halted due to high numbers experiencing a ≥10% increase in LVESV (29%; 4/14) in the sildenafil group in 6 months compared with 13% (1/8) in the placebo group. There we no statistically significant differences in outcome measures between treatment arms.
Raman 2015[20] RCT	42 DMD boys, (20, Eplerenone, 22, placebo)	Eplerenone in addition to background therapy in patients with early myocardial disease	Eplerenone - 14.5 years Placebo - 15.0 years	7 or above	At six months there were no significant difference between the eplerenone and placebo in imaging and blood biomarkers from baseline, however at 12 months the change from baseline was significant for left ventricular strain and ejection fraction and ESV, this implies that at least 6 months of the treatment drug are needed to significantly reduce the cardiac decline.
Buyse 2011[21] RCT	21 boys	Idebenone or placebo	Treated 13.4 years Placebo 10.8 years	8-16 years	No significant differences were found between idebenone and placebo group for cardiorespiratory failure.
Exercise treatment					
Jansen 2013[23] RCT	30 boys	Assisted bicycle training or no treatment	10.5 years (mean)	≥ 6 years	24 weeks: total motor function measure was stable in intervention group but had significantly decreased in the control group. No significant differences were found for six minute cycling test (A6MCT), no serious adverse events were reported.

Scoliosis treatment					
Suk 2014[24] Non randomised comparative study	66 DMD patients, minimum follow – up of two years	Surgical or non-surgical treatment for scoliosis	Surgical 14.9 years Non-surgical 14.8 years	NR	At the final evaluation, measures of spinal curvature (Cobb angle, lumbar lordosis, and pelvic obliquity), were significantly improved in the surgical group compared with the nonsurgical group (p = 0.007, 0.005, and <0.001, respectively). Mean Cobb angle: surgical group = 36.2◦ ± 16.1◦, nonsurgical group = 106.1◦ ± 122.3 (p = 0.007) Lumbar lordosis: surgical group = 37.9◦ ± 18.2, nonsurgical group = 18.4◦ ± 34.3◦ (p = 0.005) Mean pelvic obliquity: surgical group = 11.4◦ ± 8.7, nonsurgical group = 29.0◦ ± 15.5◦ (p < 0.001)
Lebel 2013 [15] Non randomised comparative study	54 ambulant boys	Glucocorticoid treatment or no treatment	Glucocorticoid - 8.5 years No treatment - 8.9 years	7-10 years	Five boys (21%) in the non-treatment group and one boy (3%) in the glucocorticoid treatment group died. At latest follow up six boys (20%) in the glucocorticoid treatment group and twenty-two (92%) in the non-treatment group developed scoliosis and underwent spinal surgery. After fifteen years of follow-up, survivors (avoiding surgery) was 78% in the treatment group and 8.3% in the non-treatment group.
Escobar-Cedillo 2013[22] RCT	20 boys, functional activity score ≤3 according to the scale described by Vignos and a maximum weight of 40 kg.	Supplementation with L-Carnitine in patients who were not undergoing steroid treatment	7 years - L- carnitine, 6 years - placebo	4-9 years old	No side effects were reported with treatment but evaluations of muscles and function showed no differences between groups.

Escolar 2012[18] RCT	64 boys, with stable dose of corticosteroids for 12 months.	Pentoxifylline (PTX) treatment with a placebo.	9.9 years (PTX) 10.2 (placebo)	7 years or older	No significant difference was found between PTX and the placebo group for total quantitative muscle testing (QMT) score (MD 0.63, 95% CI 0.21 to 1.48, P=0.14). The secondary outcomes also failed to detect any significant differences between the groups for the mean QMT subgroup scores, MMT, functional grading, PFTs, degree of contractures, timed function test, and PedsQL scores. A difference was found in the timed 10-m run/walk test where the PTX group showed significantly less decline in the velocity to perform the 10-m timed run/walk test after 12 months compared to the placebo group, 0.1 m/second vs 0.3 m/second, respectively.

References

1. Bushby K, Finkel R, Birnkrant D, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychological management. The Lancet Neurology. 2009;9(1):16.
2. Duchenne and Becker muscular dystrophy [Internet]. U.S. National Library of Medicine; [updated Jul 19 2015]. Available from: http://ghr.nlm.nih.gov/condition/duchenne-and-becker-muscular-dystrophy.
3. Pollitt R, Green A, McCabe C, et al. Neonatal screening for inborn errors of metabolism: cost, yield and outcome. Health Technol Assess. 1997;1(7).
4. Moat SJ, Bradley DM, Salmon R, et al. Newborn bloodspot screening for Duchenne Muscular Dystrophy: 21 years experience in Wales (UK). Eur J Hum Genet. 2013;21(10):1049-53.
5. Ross L. Screening for conditions that do not meet the Wilson and Jungner criteria: the case of Duchenne muscular dystrophy. Am J Med Genet A. 2006;140(8):914-22.
6. Mendell JR, Shilling C, Leslie ND, et al. Evidence-based path to newborn screening for duchenne muscular dystrophy. Ann Neurol. 2012;71(3):304-13.
7. Hu J, Kong M, Ye Y, et al. Serum miR-206 and other muscle-specific microRNAs as non-invasive biomarkers for Duchenne muscular dystrophy. J Neurochem. 2014;129(5):877-83.
8. Bushby K, Finkel R, Wong B, et al. Ataluren treatment of patients with nonsense mutation dystrophinopathy. Muscle Nerve. 2014;50(4):477-87.
9. Finkel RS, Flanigan KM, Wong B, et al. Phase 2a study of ataluren-mediated dystrophin production in patients with nonsense mutation Duchenne muscular dystrophy. PLoS ONE. 2013;8(12).
10. Flanigan KM, Voit T, Rosales XQ, et al. Pharmacokinetics and safety of single doses of drisapersen in non-ambulant subjects with Duchenne muscular dystrophy: Results of a double-blind randomized clinical trial. Neuromuscul Disord. 2014;24(1):16-24.
11. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013;74(5):637-47.
12. Voit T, Topaloglu H, Straub V, et al. Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): An exploratory, randomised, placebo-controlled phase 2 study. Lancet Neurol. 2014;13(10):987-96.
13. Escolar DM, Hache LP, Clemens PR, et al. Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy. Neurology. 2011;77(5):444-52.
14. Karimzadeh P, Ghazavi A. Comparison of deflazacort and prednisone in duchenne muscular dystrophy. Iran J Child Neurol. 2012;6(SUPPL. 1):5-12.
15. Lebel DE, Corston JA, McAdam LC, et al. Glucocorticoid treatment for the prevention of scoliosis in children with Duchenne muscular dystrophy: Long-term follow-up. J Bone Joint Surg Am. 2013;95(12):1057-61.
16. Sato Y, Yamauchi A, Urano M, et al. Corticosteroid therapy for duchenne muscular dystrophy: Improvement of psychomotor function. Pediatr Neurol. 2014;50(1):31-7.
17. Allen HD, Flanigan KM, Thrush PT, et al. A randomized, double-blind trial of lisinopril and losartan for the treatment of cardiomyopathy in duchenne duscular dystrophy. PLoS Currents. 2013;12(5).

18. Escolar DM, Zimmerman A, Bertorini T, et al. Pentoxifylline as a rescue treatment for DMD: A randomized double-blind clinical trial. Neurology. 2012;78(12):904-13.
19. Leung DG, Herzka DA, Thompson WR, et al. Sildenafil does not improve cardiomyopathy in Duchenne/Becker muscular dystrophy. Ann Neurol. 2014;76(4):541-9.
20. Raman SV, Hor KN, Mazur W, et al. Eplerenone for early cardiomyopathy in Duchenne muscular dystrophy: A randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2015;14(2):153-61.
21. Buyse GM, Goemans N, van den Hauwe M, et al. Idebenone as a novel, therapeutic approach for duchenne muscular dystrophy: Results from a 12 month, double-blind, randomized placebo-controlled trial. Neuromuscul Disord. 2011;21(6):396-405.
22. Escobar-Cedillo RE, Tintos-Hernandez JA, Martinez-Castro G, et al. L-carnitine supplementation in duchenne muscular dystrophy steroid-naive patients: A pilot study. Curr Top Nutraceutical Res. 2013;11(3):97-101.
23. Jansen M, Van Alfen N, Geurts ACH, et al. Assisted bicycle training delays functional deterioration in boys with Duchenne muscular dystrophy: The randomized controlled trial "no use is disuse". Neurorehabil Neural Repair. 2013;27(9):816-27.
24. Suk KS, Lee BH, Lee HM, et al. Functional outcomes in Duchenne muscular dystrophy scoliosis: comparison of the differences between surgical and nonsurgical treatment. J Bone Joint Surg Am. 2014;96(5):409-15.
25. Wood MF, Hughes SC, Hache LP, et al. Parental attitudes toward newborn screening for Duchenne/Becker muscular dystrophy and spinal muscular atrophy. Muscle and Nerve. 2014;49(6):822-8.
26. Wong SH, Archibald AD, McClaren BJ, et al. 'There's no easy answer': Age at diagnosis of boys with Duchenne muscular dystrophy and parent's views on population screening. Twin Research and Human Genetics. 2011;14(4):384.
27. Wong SH, McClaren BJ, Archibald AD, et al. A mixed methods study of age at diagnosis and diagnostic odyssey for Duchenne muscular dystrophy. European Journal of Human Genetics. 2015.