EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2016
EMA/30262/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy' (EMA/CHMP/236981/2011)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	TREAT-NMD Alliance
2	1. Action Duchenne, Alex's Wish 3. Duchenne Children's Trust 4. Duchenne Now 5. Harrison's Fund 6. Joining Jack 7. The Duchenne Research Fund (all non-profit charities and trusts based in England with the objective of funding work and clinical trials to cure and treat Duchenne Muscular Dystrophy)
3	Prosensa
4	Pfizer Inc
5	EFPIA – Pär Tellner
6	Craig M. McDonald, MD, Director National Institute of Disability and Rehabilitation Research (NIDRR) Rehabilitation Research & Training Center on Neuromuscular Diseases
7	Institut des Biotherapies/AFM-Telethon
8	Italfarmaco S.p.A.
9	Domenico Criscuolo on behalf of IFAPP (International Federation of Associations of Pharmaceutical Physicians)
10	Andrew and Alex Johnson. Parents of a child with DMD
11	Paul Ackroyd
12	John Gorman
13	Nick Catlin
14	Anonymous
15	Emily Crossley, mother of Eli Crossley, age 6, with Duchenne muscular Dystrophy

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1. General comments – overview

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1	The TREAT-NMD Alliance, in collaboration with stakeholders in the neuromuscular field, welcomes the opportunity to comment on these draft guidelines. A TREAT-NMD workshop hosted by the EMA, on September 25th 2009, discussed the development of antisense oligonucleotide therapies for DMD, and a workshop report was published in 2010 (Muntoni et al., 2010). This workshop included discussions regarding outcome measures for clinical trials in DMD, and over the last 2-3 years substantial data has been gathered and published in regard to the 6MWT and other outcome measures in DMD. This work has included substantial input from various patient organisations, which have helped to contribute to the current knowledge of these measures and the clinical meaningfulness of their use in clinical studies with a number of different therapeutic strategies. Duchenne MD patient organizations have contributed to a more efficient drug development process, becoming partners in care, research and drug development; willing to shoulder responsibility and contribute towards advancing treatments and a cure. Some organizations have started their own research institutes, and others have invested in extramural research, clinical centres and industry to develop viable treatments. Collaboration with patient organisations at all stages of the therapeutic development process has led to a speedier transfer of promising technology from the laboratory into clinical trials and will in future ensure that approval of and access to effective treatments will be addressed with the utmost urgency warranted by the severity of the condition. Duchenne Muscular Dystrophy is a progressive disorder where	It is completely agreed that there is a high medical need and there should not be any discrimination between patients with more frequent and less frequent mutations, low and high disease severity, or young children, ambulant and non-ambulant boys. In this respect extrapolation is discussed in section 7.7 of the guideline. However, as this is a case by case decision, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.

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	patients lose muscle fibres, causing muscle breakdown every single day and at all ages. This muscle breakdown leads to progressive loss of function, one function after another. In general, one could state that slowing down or stopping the progression of the disease is the most meaningful to patients because it preserves their quality of life, delaying by months or years the next loss of function. For the younger patients, being able to walk, to stand, to be able to get up from the floor after a fall or to fall less; to have enough arm strength to open a door or to lift one's arms to reach for an object; simple tasks, but activities of daily living that are important to preserve as long as possible. Maintaining the ability to walk is a priority which seems quite obvious but it is important to recognize that when it becomes impossible to walk up or down one or more steps, the individual will also be unable to step off a curb, walk across the street and enter buildings with even a small threshold. If unable to get up from the floor, significant independence is lost as it then becomes unsafe for the individual to be alone, without assistance. The loss of these abilities impacts the school experience, increases the risk as well as the fear of falling. Losing the ability to stand further compromises the quality of life. It means the loss of the ability to transfer from chair to the toilet, from the bed to the chair, from chair to the car. With the loss of ambulation, stability of the trunk and arm function becomes very important to maintain. Arm function impacts the ability to manoeuvre the chair, to eat, to comb hair, to brush one's teeth, to take care of the simple tasks of everyday life. Hand function is a bridge to prevent the social isolation that accompanies progressive, debilitating diseases. Preserving the ability to turn over while in bed is important as this has a major impact on the entire family. Losing this ability	

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	necessitates a member of the family to wake several times each night, often between 6 and 10 times, to reposition the individual which leads to a great deal of lost sleep and increased stress for both the patient and the parent. In adolescents and adults, coughing is essential to clear the airway and to maintain respiratory function. The inability to cough indicates increased weakening of the muscles of respiration. As a result, significant complications and death may result from infection and pulmonary complications. Finally, muscles become too weak to properly ventilate the lungs; night time ventilation is required and will ultimately be needed around the clock. The lack of dystrophin has a negative impact on the heart as cardiomyocytes are replaced by fibrous tissue and fat, which leads to rhythm abnormalities and right sided heart failure. In progressive debilitating diseases such as DMD, the loss of function ripples throughout the family as primary caregivers and other family members accommodate for the loss. The result is social isolation of the family as well as financial distress, as families struggle to cover expenses due to loss of income as a family member will necessarily be needed to provide the required comprehensive care. Individuals with DMD want and need to be productive members of society. It is important to realize that small changes, stabilization of disease no matter the age or degree of function would make a meaningful difference in the lives of these patients and their patients, dramatically impacting the way these individuals feel, function and survive. The Duchenne community fears drugs currently in the pipeline, when showing safety and positive results, will only be allowed for a narrow label; that is, limited to the subset of patients tested during the trial. Young children and non-ambulant boys and men may have to	

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	wait many more years if a full dataset is required through a phase 3 clinical trial. Drugs are approved on data and not on emotions but *high medical need seems to counterweigh uncertainties about the scientific evidence in the benefit-risk assessment of OMPs (Putzeist, 2012)** The Duchenne Community believes it is essential to underline the high medical need as well as the risk of doing nothing. In rare, progressive, debilitating, life limiting conditions, there are very few or no options. Patients lose muscle fibres every day from birth on (young children already having CK levels above 20.000 IU/L, normal range is generally up to 250 U/L, showing massive muscle breakdown, is typical) which results in loss of function. Opportunities to slow or halt disease progression are severely limited or non-existent. Older boys and men with DMD still consider their lives as very valuable. In adults, with little remaining muscle and severely limited function, it does not mean it is not important to treat them. On the contrary, for them, maintaining the ability to use their hands is crucial. To use a joystick as well as their computers, gives them the opportunity to work and communicate. Here is what some patients have to say: Robert (age 28) “Keeping as much functionality in my hands as possible is vital to me, it is really the only part of my body that has any strength left in it. It means I still have a little bit of independence left, because they enable me to still drive my chair with ease meaning I can go out with friends and family without having to rely on someone pushing me. I also participate in powerchair football, which is the only physically active sport that I am able to play and it is a good chance to socialise, but if my hands became too weak to drive my chair I would	

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	be unable to participate in this sport. I can still clean my teeth, I can still text my friends, and once I have been set up at my computer I can surf the Internet, chat with friends, send emails and play my favourite games all without any assistance, meaning I feel a sense of independence. Being able to go on the internet and chat with my friends is vital for helping me socialise, particularly in the cold winters when I am unable to get out the house so often and this would increase my isolation further still. I then would be 100% dependent on others for every single little thing and I would be very isolated from the outside world, and this would be very hard to deal with." Mark (age 43) "Keeping what limited hand movement I have, particularly in my right hand is extremely essential in maintaining independence. Whilst it may not be one of the life threatening aspects of my condition it is vital to many of the activities I carry out every day. The hand movement I have allows me the freedom to control my chair and operate my computer, thus keeping what little independence without assistance I have. When you need assistance with almost everything it's very liberating to do a few things yourself. However, when my hand is cold I completely lose all function which is very frustrating and extremely debilitating. Anything which could avoid losing hand movement would obviously be hugely beneficial to myself and many others." Jon (age 31) "Improved hand strength has a huge impact on the ability to people with DMD to maintain a degree of independence and carry out activities of daily living. The ability to control a wheelchair	

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	independently is greatly enhanced by improved hand strength, without which individuals can lose the ability to get out and about, particular in cold weather, and may be isolated in their homes. Improved hand strength also vastly improves an individual's ability to use a computer, which is often a window to the world for people who may be isolated and is a social lifeline. The ability to use a mouse or keyboard can enable individuals to engage in gaming, one of the few interactive leisure opportunities available to adults with DMD which can have a huge impact on wellbeing." Extrapolation of data gathered in other groups of patients should be considered as an important opportunity for the Duchenne community. We are also encouraged by the on-going discussions about 'adaptive approaches' to clinical research, including extrapolation of data and hope the DMD patients can benefit from new recommendations in the very near future (please refer to de Jong et al., Nature Reviews Drug Discovery, Vol 12, September 2013, pp 647-648). * Drug Discov Today. 2012 Apr;17(7-8):352-8. doi: 10.1016/j.drudis.2011.10.027. Epub 2011 Nov 7. **Determinants for successful marketing authorization of orphan medicinal products in the EU.** Putzeist M, Heemstra HE, Garcia JL, Mantel-Teeuwisse AK, Gispen-De Wied CC, Hoes AW, Leufkens HG. Utrecht Institute for Pharmaceutical Sciences, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, The Netherlands.	
2	The Guidelines do not appear to recognise or alternatively place insufficient weight on the severity of DMD if the natural course of the condition is untreated. Even with the current treatments available, it	The severe and fatal character of the disease is very well known and recognized, as well as the urgent need for the development of possible treatments. This may not be

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	is a condition for which there is currently no cure of effective treatment. DMD is guaranteed to lead to early death and is guaranteed to result in significant physically impaired quality of life from a very early age.	obvious from the text of the guideline due to the formal style in which it is written similar to all other guidelines many of which discuss the development of medicinal products for other severely debilitating, devastating and fatal diseases.
2	In the context of 1 above, (and as the Guidelines acknowledge at lines 48 and 49), Exon skipping and other genetic based interventions have made great advances and offer realistic therapeutic options for patients in the foreseeable future.	The development of approaches for treating the disease have been encouraged through several dialogues between regulators and other stakeholders not only during workshops but also in the form of scientific advice, etc.
2	Given that children are suffering and patients are dying, it is imperative that EMA do not treat the Guidelines as a process the consequence of which will be to harm or delay the development of these potentially live saving and life enhancing treatments which will not only improve the lives of patients but also their families and also have a dramatic impact on the savings that will be made to the public purse once these patients are less dependent of state assisted care.	The flexibility and discussions about a possible limited package for assessment have been ongoing. In this respect extrapolation is discussed in section 7.7 of the guideline. However, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.
2	Whilst it is acknowledged that EMA and the regulators must carry out their invaluable role the Guidelines do not strike a proper risk-benefit balance. They tacitly discourage the use of surrogate end points and biomarkers as outcome measures. That is substantially prejudicial to the development of the stated therapies and harmful to DMD patients.	While it is agreed that restoration of dystrophin in muscle is a valid PD endpoint (at least for those products aiming at dystrophin restoration), latest experience has confirmed that this has to correlate to functional outcomes which are important for the patient. A DMD patient would not be interested if there is a signal of dystrophin in the muscle biopsy unless he can notice that he is able to do more than before treatment or at least that he is not deteriorating as could be expected. Establishing B/R on biomarkers may include some risk if the correlation between a biomarker and a clinical outcome is not well investigated and established,

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		because it may result in approval of compounds which do not have any clinical effect for the patient.
2	As is trite, despite significant medical advances, there is much about DMD which is still unknown. The current generation of Duchenne children need to be treated and are being ignored by these Guidelines. It is submitted that the Guidelines should be open minded to surrogate end points and biomarkers as outcome measures on the understanding that studies will be supported by longer term extension studies with end points more akin to the physical based ones referred to in the Guidelines. That is surely the most humane and ethical way to proceed in circumstances where the condition is an urgent unmet medical need.	The accelerate pathways for registration are still available as discussed in 2009. With regard to dystrophin it is explicitly mentioned that it is an accepted biomarker for proof of PD effect (in products with mechanism of action inducing dystrophin production), but is not recommended as surrogate marker to measure efficacy, since quantification and therefore measurement of change is problematic. In addition the finally important outcome for the patients is any clinical meaningful change. Therefore dystrophin is not accepted as a primary efficacy endpoint in phase 3 studies.
2	At a meeting on 25 September 2009 a group of 98 DMD experts assembled by Treat NMD met at the London offices of EMA (or EMEA as it was then) to begin a dialogue on regulatory issues surrounding AONs. EMA representatives included the chairs and members of the committees for Human Medicinal Products, Paediatrics, Advance Therapies, Orphan Drugs as well as members of the Scientific Advice Working Party and senior members of the EMA secretariat. During that meeting, EMA representatives indicated that they would be willing to be flexible and to engage in detailed discussion regarding the development of a regulatory pathway for approval of Exon Skipping. The regulatory experts stressed that they were willing to discuss alternative ways forward for very small populations. It was noted that it may not be necessary to do separate studies for each Exon but much data can be shared and/or data can be extrapolated and all matters would be looked at upon a benefit – risk balance. Furthermore, it was stressed that there are fast regulatory	The possibility for extrapolation is discussed in the GL and has been amended. Please note that the GL is aimed for all possible medicinal products for the treatment of DMD and not specifically only for the exon skipping approach.

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	procedures for approval for medicinal products especially if they are lifesaving and there is an unmet medical need. These Guidelines therefore contradict the flexible and progressive approach endorsed by EMA previously.	
2	The Guidelines acknowledge that the heterogeneity in phenotypes of DMD is such that there are many differences in the treatments that may be required by patients. Despite this, the Guidelines dictate prescriptive regimented inflexible approaches to outcome measures.	As stated above since the GL is prepared to provide guidance on general principles in the development of any medicinal products for the treatment in DMD (symptomatic, disease modifying) a balance between not being too specific and providing some general principle requirements is sought. However, it has been stated that the primary outcome measures could be different according to the treatment goal, the mechanism of action of the compound and the target population (sections 6.2. and 7.5.1.)
2	The Guidelines accept that biomarkers are effectively used for the diagnosis of BDMD. They also accept that BDMD are caused by a lack of dystrophin. Therefore to publish guidelines dismissing (at least tacitly) the creation of dystrophin as an effective primary endpoint is hypercritical and potentially unfair and harmful to DMD patients.	Please refer to comment above.
3	Prosensa Therapeutics B.V. welcomes the opportunity to comment on this draft guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy. Prosensa Therapeutics B.V. is a biotechnology company focused on the discovery, development and commercialization of RNA-modulating therapeutics. The company targets genetic disorders with a large unmet medical need, with a focus on neuromuscular and neurodegenerative disorders, such as Duchenne Muscular Dystrophy, Myotonic Dystrophy and Huntington's disease.	**Comment acknowledged.**

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4	Pfizer Inc. is appreciative of the EMA's efforts to develop these draft guidelines and is grateful for the opportunity to provide feedback. Duchenne muscular dystrophy (DMD) is a disease with significant unmet need and an indication that may benefit from therapeutic advances in the very near future. It is a progressive, fatal disease with a well-known underlying genetic cause, the loss of dystrophin. The effects of the loss of dystrophin production are complex and present in many diverse ways that reduce quality of life and eventually result in death. Thus, any therapy that is able to slow disease progression via either disease correction (dystrophin replacement (by e.g. antisense oligonucleotides, read through compounds, or utrophin upregulation) or disease modification (anti-fibrotics, anti-inflammatories, or muscle anabolics) should be advanced with the goal of improving quality of life. The various approaches for the treatment of DMD/(Becker muscular dystrophy (BMD) must be factored into outcome measures to evaluate the effectiveness of treatment. Significant effort has been applied to develop appropriate, meaningful measures that could be validated as clinically meaningful. Clear regulatory guidance will be valuable in accelerating drug development for this severe disease.	**Comment acknowledged.**
5	We appreciate the role of genetic testing to confirm the diagnosis of DMD and BMD, however, the genotype may not necessarily correlate to phenotypic expression of the disease and therefore genetic testing for diagnosis and inclusion in clinical trials should be supported by diagnosis through clinical signs (See later comment on lines 185-188 & lines 198-199). More emphasis should be made to stress the role of heterogeneity within populations of DMD and BMD patients.	**Not endorsed.** Section 5.2 Inclusion criteria, describes, that due to the existing heterogeneity between DMD and BMD, these populations should be studied separately.
5	The guideline focuses on a generic approach to address the needs of patients with DMD or BMD, however, more emphases should be given	**Not endorsed.** Due to the current situation with increasing knowledge based on the ongoing clinical programmes for

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	to other approaches especially given the numerous targets which may be addressed with many different mechanisms of action (e.g., dystrophin protein replacement, anti-inflammatory, utrophin upregulator, calcium modulators, myoblast/stem cells, etc.). This is particularly the case for BMD to ensure this group of adult patients is not neglected as BMD is rarer than DMD and clinically more heterogeneous. In particular interventions that promote muscle growth factor modulation, cell-based therapies, therapies that reduce the inflammatory component in muscle or perhaps target cardiomyopathy would be especially appropriate to test in the BMD population.	DMD, specific recommendations in this guideline mostly refer to DMD but some of these might also be applicable for BMD. For mechanism of action and treatment target, please refer to sections 6.2. and 7.5.1.
6	We applaud the efforts of the European Medicines Agency to develop a guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy. It is apparent that a rather thorough review of the literature has been conducted but much new information has recently been published from 2010 to 2013 (both before and subsequent to the development of the draft Guidelines) that produced data and concepts that are highly relevant to DMD and BMD clinical trials. There are two substantial issues that are most problematic with the guidelines that I previously presented to representatives from advocacy groups, academicians, industry, industry, and representatives from the EMA in London, UK on 21 June 2013. The first involves the omission of published data pertaining to the reliability, validity, MCID, and clinical meaningfulness of the 6-minute walk test as a clinical endpoint for Duchenne muscular dystrophy. Literature strongly refutes a learning effect in the measure, substantiates the validity of the 6MWT as a measure of disease progression, substantiates the minimal important difference or minimal clinically important difference in DMD (30 meters) based on statistical distribution properties, prediction of 10% progression in	Point 1: **Not accepted**. The inclusion of the minimal clinically important difference (30 meters) on the 6MWT is beyond the scope of this guideline. See comments below. Point 2: **Accepted**. The guideline does not request for co-primary endpoints any longer. However, for total evidence of clinical efficacy an effect on motor function should be supported by an effect on muscle strength. Two endpoints should be selected from the domains muscle strength and motor function. One should be selected as primary endpoint and the other as secondary endpoint.

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	ambulatory function over 1 year (predictive of loss of ambulation at 4 years), the direct ability of 30 meter decrements in 6MWD to directly predict loss of ambulation over 1 and 2 years, and confirms a strong relationship between the 6MWT and patient-reported outcomes (PROs) which focus on activities of daily living, basic mobility and transfers, and sports and physical functioning. Further longitudinal data confirm the 6MWT to be a more sensitive measure of disease progression than quantitative strength and time function tests. Second, the recommendation that both strength and function be used as co-primary endpoints is a profound concern because of the logarithmic (non-linear relationship between strength and function in DMD. Knee extension has been shown to be the lower extremity strength most closely associated with ambulatory function. Early in the ambulatory phase (4 to 7 years) large decrements in strength are associated with little change in function. Later in the ambulatory phase very large changes in ambulatory function occur with relatively minimal changes in knee extension strength. Strength may be an appropriate endpoint for therapeutics leading to short-term benefit in terms of increased force production of fibers. Strength does not appear to be an appropriate endpoint for clinical trials of therapeutics that stabilize functional loss without changing strength (e.g. dystrophin restoration). It would be better not to dilute the effect on the most sensitive and meaningful primary endpoint (function) by adding a pre-specified co-primary endpoint that is not as sensitive (strength). Better not to dilute the effect on the most sensitive and meaningful primary endpoint (function) by adding a pre-specified co-primary endpoint that is not as sensitive (strength). Natural history data do not support the recommendation for co-primary endpoints involving strength and function and surveys from advocacy groups	

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	presented in the London meeting indicate that function is always more important to patients and families as compared to strength. Thus this recommendation will be extremely counterproductive to clinical trials in ambulatory DMD while insufficient data exist in non-ambulant patients.	
7	This guideline on the clinical investigation of medicinal product for the treatment of BMD and DMD is very important for us. It will help us for the development of new medicinal products to treat these orphan diseases. In this draft guideline we are however missing considerations regarding the evaluation of upper limb strengths and function and the quality of life assessment that is linked to. This conclusion is the rational for the comments and propositions of changes below.	**Accepted.** Recommendations have been included.
9	The announcement of the preparation of this guideline was distributed for comments in June-September 2011: it was stated that the complete guideline was going to be released for consultation by Q2 2012. It is a pity that this guideline, which refers to a life threatening condition affecting mainly boys and girls in the paediatric age, is released for consultation with a delay of about one year.	**Not endorsed**. Due to the tremendous progress in this field it was decided to postpone this guideline. This delay also allowed the critical review and use of all recently generated data on the disease. In the meantime companies were invited to come to scientific advice to discuss their specific programmes, which allowed specific advice for each compound under development for DMD.
10	In October 2011 we received the shattering news that our five year old son Jack has Duchenne muscular dystrophy (DMD). Failing a medical breakthrough, Jack's life will follow a predetermined path, mapped out by this progressive muscle wasting condition. In short, he will no longer be able to walk by the time he reaches adolescence and will lose the use of every single muscle in his body thereafter. He may need spinal rods to keep him upright and ventilation to help him breath. Eventually his heart and lungs will fail and he will die,	This presents a very typical example of the problems which patients (and their families) with a rare mutation do face. It is completely agreed that there should not be any discrimination between patients with more frequent and less frequent mutations. In this respect extrapolation is discussed in the guideline. However, as this is a case by

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	probably in his 20s. Jack is blissfully unaware of his condition and dreams of one day being a rugby player like his dad. There are no words to describe the utter devastation felt upon hearing that your child's life will be cut short because there is currently no treatment available. We have had the greatest pleasure watching Jack develop into the amazing fun loving boy he is today but now, unbelievably, we must prepare ourselves for his steady decline. For us the worst part is knowing there are a number of potential treatments in the pipeline for DMD that could see him stabilize and preserve his muscle function but not knowing if he will ever be allowed to benefit from them. We understand that information is needed to make sure they are working safely and effectively but we are very worried that in the strive for such information, the people involved do not lose sight of how devastatingly awful the natural history of DMD is, even some small benefit to our children is better than nothing. We pray every day that these potential treatments are accelerated through the approval process and made available for those living with DMD today. Exon skipping is one breakthrough approach that has the potential to treat patients with deletions. Our son would potentially benefit from an AON being developed for his exon. He has a rare exon and under current regulations it would be difficult for the drug companies to develop a AON to correct his deletion. Current legislation means that each medicine has to be developed as though it was a completely separate entity and not part of a specific drug/chemistry family and the regulatory processes differ between jurisdictions. This means that under today's conditions there will be a gap of many years between the availability of the first medicine and the complete series of drugs needed to make the exon-skipping tool kit required for all boys who could potentially be treated. Such a situation opens up the real likelihood of discrimination by genetic mutation, with some boys receiving treatment while others with a different mutations are left untreated. The situation is even more acute for individuals like our son with a very	case decision, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.

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	rare mutations. Medicines currently under development only address the most common mutations in the 'hot spot' of the dystrophin gene – affecting approximately 40% of boys with DMD. Other mutations are extremely uncommon, for example out of a UK population of 60 million only a handful of boys require the skipping of exons 18 or 35. As parents this is a heartbreaking situation for us to be in because we can see a treatment insight but drug companies are unwilling to manufacture the drug under current regulations. The severity of DMD, the unmet need for treatment, the rarity of the condition and the novelty of the therapeutic approach (i.e. the use of customized variants of similar medicines to treat all those likely to benefit) requires a new regulatory roadmap. Because of the progressively smaller populations that could be treated using individualized exon-skipping drugs, a full clinical development plan for each drug would be impossible because of the small patient numbers. A more 'staggered' approval approach could be envisaged for the described rarer exon treatments where information gained from the larger populations treated by exon skipping drugs could supplement the regulatory filing so that there would eventually be a 'platform' approval which would require a much less stringent regulatory pathway for the newer follow-on exon drugs. A platform of data generated across numerous exon skipping programs using pre-clinical, biomarker based clinical efficacy, clinical pharmacology, chemistry and manufacturing data, would be used to stream line the regulatory process allowing approval for similar drugs differing only in the sequence and containing and identical backbone chemistry. Such an adaptive approach could seek to maximize the positive impact of these new drugs on public health by balancing timely access for patients with the need to provide adequate evolving information on benefits and risks. The initiation of clinical trials can be a time-consuming process, especially for rare diseases. Once the first exon-skipping compound of a particular class has been approved by regulators, can placebo arms in	

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	clinical trials be removed? As a parent I feel they are unethical and could hinder trial recruitment. When dealing with rare exons there will be a small placebo group which may provide misleading information. Can external control groups within clinical studies be adopted? All our children need access to these drugs now. Owing to the progressive nature of DMD, boys at different ages have varying capabilities that can be measured while assessing the effect of treatment. Currently, clinical studies are conducted primarily in boys who can still walk ('ambulant' individuals) because only this subpopulation has a validated clinical endpoint – the 6-minute walk test, which measures the distance a person can walk within a 6-minute time frame. As the underlying genetic defect (lack of dystrophin) is common, it is proposed that once the efficacy and safety of a medicine has been demonstrated in different subpopulations (e.g. ambulant, non-ambulant, the very young) for one drug programme, the effects in the ambulant population can be extrapolated to other patient groups for subsequent drugs. As AONs are designed for rare mutations, although supportive information will be available from preceding compounds, AONs will be approved with comparatively little data due to the small patient population. The urgency with which these are supplied will also have an impact on the amount of accompanying data – the faster the AON is made available the less the data. So there is an important discussion to be had on risk/benefit. Due to the rarity of these mutations the impact on public health will be minimal. An analogy is the influenza (flu) vaccine. Each year a new vaccine similar to the previous year's vaccine is produced, the difference being the targeting molecules which address that year's strain of flu virus. However, unlike the flu vaccine, which will be administered to millions of people in a country, the DMD medicine will only be given to a handful of individuals with this rare but lethal disease. Thus, the impact on public health is quite different. In addition, unlike a flu vaccine this medicine will need to be given regularly over many years. The risk for us is the risk of doing	

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	nothing and watching our son lose every ability has gained. Please allow the Duchenne patient community to be actively involved together with their physicians, regulators and politicians in defining the appropriate level of risk given the severity of the disease and assumed benefit from the treatments.	
11	The Guidelines do not appear to recognise or alternatively place insufficient weight on the severity of DMD if the natural course of the condition is untreated. Even with the current treatments available, it is a condition for which there is currently no cure of effective treatment. DMD is guaranteed to lead to early death and is guaranteed to result in significant physically impaired quality of life from a very early age.	The severe and fatal character of the disease is very well known and recognized, as well as the urgent need for the development of possible treatments. This may not be obvious from the text of the guideline due to the formal style in which it is written similar to all other guidelines many of which discuss the development of medicinal products for other severely debilitating, devastating and fatal diseases.
11	In the context of 1 above, (and as the Guidelines acknowledge at lines 48 and 49), Exon skipping and other genetic based interventions have made great advances and offer realistic therapeutic options for patients in the foreseeable future.	The development of approaches for treating the disease have been encouraged through several dialogues between regulators and other stakeholders not only during workshops but also in the form of scientific advice, etc.
11	Given that children are suffering and patients are dying, it is imperative that EMA do not treat the Guidelines as a process the consequence of which will be to harm or delay the development of these potentially live saving and life enhancing treatments which will not only improve the lives of patients but also their families and also have a dramatic impact on the savings that will be made to the public purse once these patients are less dependent of state assisted care.	The flexibility and discussions about a possible limited package have been ongoing. In this respect extrapolation is discussed in section 7.7 of the guideline. However, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.
11	Whilst it is acknowledged that EMA and the regulators must carry out their invaluable role the Guidelines do not strike a proper risk-benefit	While it is agreed that restoration of dystrophin in muscle is a valid PD endpoint (at least for those products aiming at

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	balance. They tacitly discourage the use of surrogate end points and biomarkers as outcome measures. That is substantially prejudicial to the development of the stated therapies and harmful to DMD patients.	dystrophin restoration), latest experience has confirmed that this has to correlate to functional outcome which are important for the patient. A DMD patient would not be interested if there is a signal of dystrophin in the muscle biopsy unless he can notice that he is able to do more than before treatment or at least that he is not deteriorating as could be expected.
11	Despite significant medical advances, there is much about DMD which is still unknown. The current generation of Duchenne children need to be treated and are being ignored by these Guidelines. The Guidelines should be open minded to surrogate end points and biomarkers as outcome measures on the understanding that studies will be supported by longer term extension studies with end points more akin to the physical based ones referred to in the Guidelines. That is surely the most humane and ethical way to proceed in circumstances where the condition is an urgent unmet medical need.	The accelerate pathways for registration are still available as discussed in 2009. With regard to dystrophin it is explicitly mentioned that it is an accepted biomarker for proof of PD effect (in products with mechanism of action inducing dystrophin production), but is not recommended as surrogate marker to measure efficacy, since quantification and therefore measurement of change is problematic. In addition the finally important outcome for the patients is any clinical meaningful change. Therefore dystrophin is not accepted as a primary efficacy endpoint in phase 3 studies.
11	At a meeting on 25 September 2009 a group of 98 DMD experts assembled by Treat NMD met at the London offices of EMA (or EMEA as it was then) to begin a dialogue on regulatory issues surrounding AONs. EMA representatives included the chairs and members of the committees for Human Medicinal Products, Paediatrics, Advance Therapies, Orphan Drugs as well as members of the Scientific Advice Working Party and senior members of the EMA secretariat. During that meeting, EMA representatives indicated that they would be willing to be flexible and to engage in detailed discussion regarding the development of a regulatory pathway for approval of Exon Skipping. The regulatory experts stressed that they were willing to	The possibility for extrapolation is discussed in the GL and has been amended. Please note that the GL is aimed for all possible medicinal products for the treatment of DMD and not specifically only for the exon skipping approach.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	discuss alternative ways forward for very small populations. It was noted that it may not be necessary to do separate studies for each Exon but much data can be shared and/or data can be extrapolated and all matters would be looked at upon a benefit – risk balance. Furthermore, it was stressed that there are fast regulatory procedures for approval for medicinal products especially if they are lifesaving and there is an unmet medical need. These Guidelines therefore contradict the flexible and progressive approach endorsed by EMA previously.	
11	The Guidelines acknowledge that the heterogeneity in phenotypes of DMD is such that there are many differences in the treatments that may be required by patients. Despite this, the Guidelines dictate prescriptive regimented inflexible approaches to outcome measures.	As stated above since the GL is prepared to provide guidance on general principles in the development of any medicinal products for the treatment in DMD (symptomatic, disease modifying) a balance between not being too specific and providing some general principle requirements is sought.
11	The Guidelines accept that biomarkers are effectively used for the diagnosis of BDMD. They also accept that BDMD are caused by a lack of dystrophin. Therefore to publish guidelines dismissing (at least tacitly) the creation of dystrophin as an effective primary endpoint is hypercritical and potentially unfair and harmful to DMD patients.	Please refer to the comment above.
12	Severity of disease	**Endorsed.** Severity of the disease is acknowledged.
12	Little known about the risk of the Gold Standard	**Not accepted;** discussion about existing treatments is beyond the scope of this guideline.
12	Little indicated about early age mortality (cardiac events)	**Not accepted;** measures of cardiac function , e.g. in DMD-associated dilated cardiomyopathy, are considered to be

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		relevant primary endpoints.
12	Time, Time, Time – Early chance at therapy is critical. Rapid progressive nature appears to be missed. Up front clarification on requirements for surrogate markers, placebo requirements etc. as opposed to years of uncertainty and vague directional hints/guidance. Surely a yarkstick is required to be reached, a goal where clarity is key.	See comment below.
12	Essential requirement for platform approval is missing, with regards to any rare disease with varied population genetics, but common natural history. Personalized medicine is being hailed as a new means to get therapies for rare diseases, yet the infrastructure to cater for it appears to be less than adequate. Means to cater for platform drug development needs to be addressed to give guidance to industry, clinicians and parents. This guidance needs to work to timeframes that the specific disease dictates and associated risk/benefit analysis accordingly.	See comments above.
12	Natural History studies, Biomarkers and correlation of dystrophin with clinical meaningful endpoints is key to be defined, agreed based on evidence to hand and openness to receive new evidence to set new criteria.	The generation of natural history data and possible surrogate endpoints is encouraged as has been mentioned in different dialogues between regulators, industry, academia and patients (Workshop 29.04.2015.). However such expectations are not to be included in a guideline since no specific recommendation can be made.
12	Clarity must be given up front on the adequacy of all elements of the trials (low numbers, placebo controlled trials, requirements for correlation of biomarkers to clinical meaningful measures). This allows early goal and objective setting. At present researchers,	See comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	clinicians add much more weight to the risk of not knowing what the EMA will indicate on a trial by trial basis.	
12	At a meeting on 25 September 2009 a group of 98 DMD experts assembled by Treat NMD met at the London offices of EMA (or EMEA as it was then) to begin a dialogue on regulatory issues surrounding AONs. The goal of that meeting was to progress clinical development for Exon Skipping and facilitate a path for personalized medicine, in the knowledge that linear sequential trials in a small population where > 60 Exon skipping antisense would be needed to treat all boys, we find ourselves with a guideline that ignores this personal requirement completely. Four year after this meeting and there appears to be no progress in understanding the lack of time, and personnel available to perform these trials.	The possibility for extrapolation is discussed in the GL and has been amended. Please note that the GL is aimed for all possible medicinal products for the treatment of DMD and not specifically only for the exon skipping approach.
12	Recent discussions with companies developing candidate drugs for exon skipping have indicated that discussions with the regulator left an open path for non placebo trials, but rather trials where boys would be compared against their baseline scores and Natural History. This appears to have been missed in these draft guidelines.	This issue has been addressed in earlier comments.
13	"Hi I'm Saul Catlin and I have Duchenne Muscular Dystrophy. Coping with this disease is sometimes hard. I can't run or play football and keep up with my mates. Now its tough getting up off the floor and when I went camping this summer my mum and dad had to help me lots even getting into the swimming pool. Despite this I enjoy school and after a lot of help I'm now doing really well. I want to go to College and maybe be an archaeologist. So my muscles are really	The frustration of patients and parents is very well understood. However it has to be pointed out that the drafted GL is aimed at providing general guidance on development of possible treatments for Duchenne Muscular dystrophy and not specifically to the exon skipping approach. In this respect the general principles for generating evidence for efficacy and safety of a new unknown compound are presented.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	important to me. I know that the new drug trials on exon skipping might be able to trick muscle cells to make dystrophin so my muscles could work better. This is going to really help with everything I want to do in the future. I would be happy to take part in a clinical trial if it means treating or curing my condition." London August 2013 My son Saul is now 13 years old and despite considerable advancements in the development of new gene therapy drugs none have so far become available as treatments for him or others. In my personal view this has much to do with unclear and muddled guidelines issued by regulatory authorities in relation to the conduct of clinical trials for personalised medicines for conditions like Duchenne. In 2009 I was invited to give evidence as part of the Treat NMD consultation with the EMA. (TREAT-NMD Workshop The Development of Antisense Oligonucleotide Therapies for Duchenne Muscular Dystrophy 25th September 2009 EMEA Headquarters, London, UK http://www.treat nmd.eu/downloads/file/EMEA%20briefing%20document%20and%20 agenda.pdf) The problem facing regulators was clearly defined in this report: "This level of personalised approach is currently without precedent for a genetic disease. It is the concern of advocacy groups that if the common path of taking new drugs into the clinic is followed for each individual AO, this will threaten the viability of this approach. It appears inconceivable to identify resources to bring 30 or more novel antisense AOs in the clinic via the traditional clinical trial pathway. A	With regard to the exon skipping strategy, the flexibility and discussions about a possible limited package for assessment of a second and next antisense oligonucleotide for exon skipping have been ongoing. In this respect extrapolation is discussed in section 7.7 of the guideline. However, as this is a case by case decision, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.

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	fresh look at the process is therefore needed to obviate this threat to a novel and promising therapy for DMD boys. We are therefore seeking to identify a pathway that will allow the safe and efficient progress of these drugs, and address the anxiety that there are otherwise significant hurdles to the further development of this potential treatment for DMD, a incurable and fatal disease." In the last 4 years considerable data has been collected for one sub group of Duchenne mutations, exon 51, in extensive controlled trials for Antisense Oligonucleotides. Some of this data has been published. Further progress is being severely hampered by regulatory authorities not defining how the full range of gene variations can be trialed in tandem or downstream without having to undergo the traditional clinical trial approach. Your current draft guidelines "Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy - EMA/CHMP/236981/2011 " recognises that: "The number of required patients to be included in clinical studies will particularly vary according to the number of affected patients. For very rare mutations it is obvious that only few patients can be studied." but you do not offer any alternative methodology for clinical trials for small subsets of Duchenne patients. Duchenne is a rare disease and subsets of mutations are therefore going to be very small in number. In the case of Antisense Oligonucleotide therapy it might be that drugs would be needed to be designed for a single patient mutation to provide maximum benefit. There is nothing in these guidelines that	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	even begins to accommodate how to trial drugs for a single patient. The trial design for personalised medicines for rare diseases can not always be the large scale " randomised, double-blind, parallel-group and possibly placebo controlled" or RCT as suggested by your guidelines line 458. In my view these new EMA guidelines need to include: 1) A recognition that medicines with identical chemical backbones but have small differences relating to specific patient gene variations need to be treated as a platform medicine. This would be the case for example for existing families of antisense olgionucleotides. 2) Platform medicines of this type will need randomised, double-blind, parallel-group and possibly placebo controlled clinical trials on a significant population relating to one gene variation subset of patients. (As is the case for exon 51 in the current Duchenne AO trials) 3) If the risk/benefit for the initial study or studies is encouraging then further studies for gene variants of the same chemical backbone can be undertaken without the need for extensive RCT. These might even be n=1 trials measuring efficacy against the natural history of individual patients and for studying any unexpected adverse events. see my article (Individual patient (n = 1) “trials” in Duchenne dystrophy Neuromuscular Disorders, Volume 21, Issue 7, July 2011, Pages 525-526 Nick Catlin, Karl Bettelheim, Iain Henderson) The current lack of clarity from regulatory bodies to the pharmaceutical industry is paralysing further developments in this field. By paving the way for pharmaceutical companies to conduct extensive trials on one sub set of patients and then rolling out	

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	personalised medicines of the same platform to individual patients in smaller well defined studies gives a safe and economic way for all patients to gain access to new gene therapies for Duchenne. At present we face the unethical and unimaginable situation where some patients with Duchenne Muscular Dystrophy will be given access to new drugs but others like my own son Saul may have to wait years for any chance for a gene therapy. The EMA can play a leading role in lifting the uncertainty that is preventing further investment and access to this new field of drug therapy and personalised medicines by making a clear statement about how industry can create the clinical trial protocols needed to advance these new and exciting therapeutic drugs.	
14	I write in the capacity of a parent of a son with DMD. I also run a patient group, the Duchenne Children's Trust, fundraising for research. You will have received specific comments in a joint submission, on behalf of the DMD patient Groups in the UK. What follows are general comments from an individual patient/parent perspective. 1. I would like the guideline to more adequately reflect the severity of Duchenne Muscular Dystrophy and the urgent unmet medical need of this disease. The emotional impact on a family of a diagnosis of DMD is truly shattering. When we were first given our son Eli's diagnosis, it was just unbearable to talk about. We could barely bring ourselves to say the word Duchenne Muscular Dystrophy - because they symbolised such devastation. We were sick with grief and heartbreak. The doctors were very bleak about the prognosis.	The severe and fatal character of the disease is very well known and recognized, as well as the urgent need for the development of possible treatments. This may not be obvious from the text of the guideline due to the formal style in which it is written similar to all other guidelines many of which discuss the development of medicinal products for other severely debilitating, devastating and fatal diseases. Please also refer to the comments above.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	While Eli played happily outside in the hospital playroom, they told us that he would be in a wheelchair by the age of 10 - unable ever to walk again. That in his teens he would gradually lose all his upper body function too. He won't be able to write - to use a computer - to hold a phone - to feed himself. In his 20s his heart will fail. He will not be able to breathe without a tracheotomy and a ventilator. He will die sometime in his twenties. His mind - already inquisitive, bright and engaged, will be unaffected. Like every boy with Duchenne, our beautiful son will be knowingly trapped in a body that is dying on him. People ask - how do you bear it? At the moment Nick and I can lose ourselves in the present: in Eli's innocence and his exuberant enjoyment of life. But there will come a time - a time in the very near future - when the present will no longer be a comfort to us. When we will begin to see this disease through our son's eyes. And when it's not just about us dealing with our own grief and despair. But about us watching him, seeing him truly begin to understand what life will be like. There will come a time when he asks: will I be in a wheelchair? And there will come a time when his body starts to give up on him. And he will know that it's happening. And there will be nothing that my husband and I can do to stop it. And the one over riding urge - necessity - of being a parent - to protect and nurture your child - will be crushed by the relentless march of this disease. How do we bear it? We bear it because we have great hopes that the huge advances made in the study of Duchenne over the last 20 years, will now	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	finally begin to deliver treatments. However we are in a race against time, to get these treatments to our son before it is too late. 2.For the first time in the history of this disease, exon skipping and other potential therapies have made great advances. 3.The guidelines need to more adequately reflect the very rapid decline of boys with DMD and the fact that we are in a race against time to get these potential therapies to our boys. 4.These treatments have been shown to slow down or stop the progression of the disease. Both of these are extremely important for patients - my son is 6 years old and ambulatory. To slow down the progression of the disease would mean he can stay walking for much longer and this will hugely improve his quality of life. 5.Given the above points, it is crucial that the EMA approach these guidelines with a view to allowing patients access to drugs as soon as possible. This will not only improve their lives immeasurably, but also relieve their families of the horrible emotional burden of watching their child deteriorate and rapidly lose every functional ability in their body. 6.Regarding the development of a regulatory pathway for the approval of Exon Skipping, the guidelines need to reflect ways forward for very small populations, and how drugs will be approved for subsequent exons. For subsequent exons, it may not be necessary to do separate studies for each Exon. Data can be shared or extrapolated and all decisions will be made on a benefit/risk balance that reflects the potentially life-saving effect of these treatments in a disease that has only very limited treatment options - which come with very bad side effects. The guidelines need to reflect that there are already fast regulatory procedures for approval for medicinal products, especially if they are life saving and there is an unmet medical need. Drugs to treat DMD	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	ought to be eligible for these fast track procedures. 7.Our son has deletion 48-54 which means that he is amenable to skipping exon 55. This is a drug that is in Prosensa's development pipeline. We would urge the guidelines to approach with openness, a consideration for platform approval of exon skipping drugs. If each exon has to be put through a phase 3 trial it will take many years for ALL boys to benefit from treatment. This is time we simply do not have. And to that end we want to plead with you to ask the regulators to look at the risk / benefit issue from the perspective of parent who have no other option, other than to watch their most precious thing in the whole world -their child - die a slow death. The current exon skipping drugs in clinical trial have very few side effects - far less than the only treatment currently on offer - that of a daily dose of steroids As parents we urge you to consider the fact that with these drugs the chemical backbone is identical and expected to behave in a similar way. Although it may not, this is unlikely and it's a risk that we are fully prepared to take.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
47 to 63	2	**Comment:** The summary does not address the general points made above. **Proposed change:** Make more explicit that EMA encourage and are prepared to be engaged in detailed discussion regarding the development of a regulatory pathway for approval of Aons etc and alternative ways forward for very small populations in an open and flexible way in recognition of the urgent unmet medical need. Furthermore it should be noted that data can be shared and/or data can be extrapolated between studies. It should be pointed out that regulators will always need sufficient data to evaluate the medicinal product and conclude on the benefit-risk balance in the context of a condition for which there is no cure and the natural course is most devastating. Sponsors should be told that they should discuss early with the regulators and agree on the trials before they are conducted. Moreover the Guidelines should make plain that there are fast regulatory procedures of approval for medicinal products especially if they are life-saving and there is an unmet medical need.	**Partly accepted**. In line with this and other comments a paragraph has been added in the executive summary indicating the need for discussion of the development plan to conclude on the most efficient strategy on generating data in this rare and devastating condition with high unmet medical need.
47 to 63	11	**Comment:** The summary does not address the general points made above.	**Partly accepted**. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Make more explicit that EMA encourage and are prepared to be engaged in detailed discussion regarding the development of a regulatory pathway for approval of AONs etc and alternative ways forward for very small populations in an open and flexible way in recognition of the urgent unmet medical need. Furthermore it should be noted that data can be shared and/or data can be extrapolated between studies. It should be pointed out that regulators will always need sufficient data to evaluate the medicinal product and conclude on the benefit-risk balance in the context of a condition for which there is no cure and the natural course is most devastating. Sponsors should be told that they should discuss early with the regulators and agree on the trials before they are conducted. Moreover the Guidelines should make plain that there are fast regulatory procedures of approval for medicinal products especially if they are life-saving and there is an unmet medical need.	
49-53	3	**Comment:** We agree with the general comments on the recent advances in basic and clinical research. In addition to the issues that are explicitly raised in this section, we would suggest that the specific challenge of extrapolation be included. As rarer and rarer exons are studied, extrapolation will become increasingly critical in the successful development of therapeutic agents for these exons. **Proposed change:** Include extrapolation as a specific	**Accepted**. Extrapolation has been included.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		example in the Executive summary.	
54	1	**Comment:** All cases of DMD have an onset in early childhood.	**Agreed.** Sentence corrected.
68	1	**Comment:** symptomatic girls are exceedingly rare.	**Accepted**, see comment below.
68	3	**Comment:** Symptomatic expression of DMD is exceedingly rare in girls **Proposed change:** The figures for incidence in girls are highly variable among publications, related to the milder and highly variable clinical presentation. However symptomatic expression of DMD is exceedingly rare in girls.	**Accepted.** Sentence has been corrected as proposed.
70 - 76	2	**Comment:** The Introduction section makes no comment on the untreated natural history of the condition and does not seem to appreciate the severity of the condition. Duchenne Muscular Dystrophy is better characterised as a muscle wasting disease for which there is no cure. The references to wheelchair dependency are vague and do not properly explain the natural course and severity of the condition. Once wheelchair bound, most patients have virtually complete body paralysis from their teens and the wheelchairs are motorised from before the teens because patients cannot use their arms. The wheelchair dependency “before the age of 13” starts from as early as the age of 7. DMD patients spend most of their lives on permanent or near permanent	**Not accepted.** The seriousness of the conditions is recognized by all stakeholders involved in the care and treatment of DMD. The purpose of the DMD GL is not to provide an extensive description of the disease pathology and clinical presentation, but guidance to pharmaceutical companies on the general requirements to be considered in developing possible treatments for the disease. In this respect the introduction is meant to be short and not replace textbooks on the condition. It is not agreed that the GL will “drive away” sponsors from their work, since every party involved in this development is very much aware of the seriousness of the disease and all particularities. No changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		ventilation. The incidences of spinal correction surgery are all too common. There is no mention of any of this but emphasis is placed on calf muscle pseudo-hypertrophy which emphasis is simply perverse in the overall scheme of the condition. **Proposed change:** The severity of the condition must be recognised by EMA and adequate weight placed on it and the need to be flexible. The Guidelines must recognise the needs of the Duchenne population of today and must not be written in language which results in sponsors and pharmaceutical companies being driven away from their valuable work in DMD.	
70 - 76	11	**Comment:** The Introduction section makes no comment on the untreated natural history of the condition and does not seem to appreciate the severity of the condition. Duchenne Muscular Dystrophy is better characterised as a muscle wasting disease for which there is no cure. The references to wheelchair dependency are vague and do not properly explain the natural course and severity of the condition. Once wheelchair bound, most patients have virtually complete body paralysis from their teens and the wheelchairs are motorised from before the teens because patients cannot use their arms. The wheelchair dependency “before the age of 13” starts from as early as the age of 7. DMD patients spend most of their lives on permanent or near permanent ventilation. The incidences of spinal correction surgery	**Not accepted.** See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		are all too common. There is no mention of any of this but emphasis is placed on calf muscle pseudo-hypertrophy which emphasis is simply perverse in the overall scheme of the condition. **Proposed change:** The severity of the condition must be recognised by EMA and adequate weight placed on it and the need to be flexible. The Guidelines must recognise the needs of the Duchenne population of today and must not be written in language which results in sponsors and pharmaceutical companies being driven away from their valuable work in DMD.	
74	1	**Comment:** a third of the patients with DMD do show cognitive or behavioural abnormalities, but these abnormalities don't deteriorate.	**Accepted.** Wording revised.
77	1	**Comment:** BMD is <u>always</u> milder than DMD	**Accepted.** See comment below.
77	3	**Comment:** Becker muscular dystrophy is always milder than DMD. **Proposed change:** Delete the word 'generally'.	**Accepted.** Sentence has been corrected.
78-79	1	**Comment:** mentions quadriceps weakness can be the only BMD symptom - this sentence is obsolete. Either describe the variation from very mild to very severe or do not give any examples (patients with only elevated CK are known as well – this seems to be just a random phenotype that is included)	**Accepted.** The sentence with respect to quadriceps weakness has been deleted. The variability of BMD has been described in an additional sentence.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: we suggest to delete this sentence and describe the variability of the disease (based on the following references: Comi et al., 1994; Angelini et al., 1994; McDonald et al., 1995; Aartsma-Rus et al., 2006)	
78-79	3	**Comment:** It is no longer accurate to identify quadriceps weakness as the only BMD symptom. **Proposed change:** Describe the variability of the disease (based on references, Comi et al., 1994, Aartsma-Rus et al., 2006)	**Accepted.** See comment above.
79-82	1	**Comment:** We suggest to replace this sentence with that below. **Proposed change:** Patients remain ambulatory for a variable period of their life and the majority are not wheelchair dependant. Most patients develop at some point in time dilated cardiomyopathy that is the most common cause of death. Mean age of death is in the mid-60s, and life expectancy is likely to improve further with improved cardiac surveillance.	**Accepted.** The sentence has been rephrased as proposed including a mean age of death from mid-60 instead of mid-40.
81-82	1	**Comment:** guideline states the mean age of death of BMD patients is mid-forties: This is not what is found in the Dutch BMD cohort – the average age of death is 51 years (range 34-89 years).	**Accepted.** Please refer to the comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: the estimated mean age of survival of BMD patients (based on a Kaplan-Meier analysis of the Dutch cohort) is 64 years.	
86	1	**Comment:** dystrophin is part of the dystrophin glycoprotein complex (DGC) that serves to link the muscle fibre cytoskeleton to the cell membrane and further to the extracelluar matrix. (The sarcoglycan complex is part of the larger dystrophin glycoprotein complex).	**Accepted.** Sentence has been rephrased as proposed.
88 – 90	2	**Comment:** The importance of the lack of dystrophin appears not to be fully understood here. It does not simply lead to a decrease in muscle strength. It leads to the death of it. **Proposed change:** refer to muscle death.	**Not accepted**. Muscle death is not considered that common term in medical literature with reference to DMD. No changes.
88 – 90	11	**Comment:** The importance of the lack of dystrophin appears not to be fully understood here. It does not simply lead to a decrease in muscle strength. It leads to the death of it. **Proposed change:** refer to muscle death.	**Not accepted.** See comment above.
91-95	1	**Comment:** Please insert the following sentence at the end of this paragraph. **Proposed change:** It is nevertheless important to realise that a genetic diagnosis in isolation and without	**Not agreed** - this article only refers to Becker Muscular Dystrophy.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the additional confirmation of dystrophin expression on muscle biopsy has a predictive accuracy of ~88% (Kesari et al., 2008).	
91-95	3	**Comment:** It is important, in addition to knowing the molecular defect, to confirm the diagnosis with a muscle biopsy demonstrating dystrophin expression. **Proposed change:** Please insert an additional sentence at the end of this section that states it is important to realize that a genetic diagnosis in isolation and without the confirmation of dystrophin expression has a predictive accuracy of approximately 88%.	**Not agreed.** See comment above.
93	12	**Comment:** Early Actin Binding domain hotspot is missed here. **Proposed change:** Include the early hotspot also	**Not accepted.** Details on the gene and protein are beyond the scope of this guideline. See also earlier comments.
96 - 102	2	**Comment:** Here the Guidelines recognise and accept that DMD/BMD is diagnosed by biomarkers (genetic testing). See general point 8. **Proposed change:** As above	**Not accepted.** There is a difference between using genetic testing for diagnostic purposes and the use of dystrophin as a biomarker. With regard to dystrophin it is explicitly mentioned that this is an accepted biomarker for proof of PD effect (in products with mechanism of action inducing dystrophin production), but not as surrogate marker to measure efficacy, since quantification and therefore measurement of change is problematic. In addition the finally important outcome for the patients is any clinical meaningful change. Therefore dystrophin is not accepted as a primary efficacy endpoint in

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			phase 3 studies.
96 - 102	11	**Comment:** Here the Guidelines recognise and accept that DMD/BMD is diagnosed by biomarkers (genetic testing). See general point 8. **Proposed change:** As above	**Not accepted**. See comment above.
97-98	1	**Comment:** we suggest to delete the sentence about other diagnostic methods, as the methods listed are either unspecific (CK, imaging) or explained further down in the text (biopsy).	**Not agreed**, however the sentence has been rephrased: *"Other supportive diagnostic methods include serum creatine kinase, muscle biopsy data and imaging modalities*".
100-102	3	**Comment:** While we agree that a muscle biopsy is inconvenient and invasive, dystrophin expression remains an important contribution to an accurate diagnosis. **Proposed Change:** Include a sentence that states that without a confirming muscle biopsy, the possible of a 10-12% chance of misdiagnosis that is based on genetic prediction alone should be considered.	**Not accepted**; cited article only refers to BMD.
102	1	**Comment:** Please insert the following sentence at the end of this paragraph. **Proposed change:** However the possibility of a 10-12% misdiagnosis based on genetic prediction alone should be born in mind (Kesari et al., 2008).	**Not accepted**. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
105-106	1	**Comment:** states that corticosteroids are not approved for treatment of DMD patients and their use is limited due to significant side effects: we do not agree with this – corticosteroid use is in the standards of care for DMD and the majority of patients in the Western World are on steroids. Steroids have been shown to influence the natural history of the disease by prolonging lifespan, and delaying the onset of cardiac and respiratory complications, as well as delaying the time to loss of ambulation. **Proposed change:** <u>This statement is not correct – please replace with the following sentence</u>. Corticosteroids are recommended treatments and are NICE approved, and when using the two most commonly used steroid regimens, prolongation of ambulation has been achieved (Ricotti et al., 2013).	**Partly accepted,** the reference (Ricotti et al 2013) only describes an observational study. The statement according to corticosteroids has been rephrased as follows: *"…. The majority of patients are treated with steroids which have shown to prolong lifespan and delay the onset of cardiac and respiratory complications, as well as delaying the time to loss of ambulation. However corticosteroids are not formally approved for treatment of this disease and their use is often limited due to significant side effects. Moreover, there is a lack of consensus regarding the best treatment scheme although recent evidences indicates that early and daily treatment is more effective than delayed or alternate day treatment schemes".*
105	2	**Comment:** It is stated that Corticosteroids "are not approved for treatment in this disease". Despite this, Corticosteroids are the main and only real treatment being offered to patients of DMD. It is irrefutable that Corticosteroid use is in abundance in DMD and that it is clearly prolonged the natural history of the condition. Regulators are allowing the use of corticosteroids in Duchenne and so surely on the grounds of consistency; similar flexibility is warranted in respect of gene therapy/ exon skipping etc.	Comment not completely understood. With respect to corticosteroids please note the following: *"…. The majority of patients are treated with steroids which have shown to prolong lifespan and delay the onset of cardiac and respiratory complications, as well as delaying the time to loss of ambulation. However corticosteroids are not formally approved for treatment of this disease and their use is often limited due to significant side effects. Moreover, there is a lack of consensus regarding the best treatment scheme although recent evidences indicates that early and daily treatment is more effective than delayed or alternate day treatment schemes".*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
105-107	3	**Comment:** While corticosteroids may not always have approved labelling for the treatment of DMD, they are the standard of care, with the majority of patients in the Western World receiving corticosteroids. They are recommended treatment and have been approved by Nice in the EU. Further, the use of steroids have been shown to influence the natural history or the disease by prolonging lifespan and delaying the loss of ambulation as well as delaying the onset of cardiac and respiratory complications. **Proposed Change:** Modify to wording to reflect that steroids are the accepted standard of care and have been shown to positively affect the natural history of the disease.	**Partly accepted.** See comment above.
105	11	**Comment:** It is stated that Corticosteroids "are not approved for treatment in this disease". Despite this, Corticosteroids are the main and only real treatment being offered to patients of DMD. It is irrefutable that Corticosteroid use is in abundance in DMD and that it is clearly prolonged the natural history of the condition. Regulators are allowing the use of corticosteroids in Duchenne and so surely on the grounds of consistency; similar flexibility is warranted in respect of gene therapy/ exon skipping etc.	**Partly accepted.** See comment above.
105 & 261	12	**Comment:** Indicating that Corticosteroids are not approved for DMD when they have been earmarked as	**Partly accepted.** See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		the Gold Standard for the disease in the Standards of care published in Lancet Neurology is misleading. While it may be true that placebo controlled randomised trials have not taken place (but as an aside are now underway), it is clear from the multitude of papers released that steroids alter the natural history of the disease. This admittedly is at a high cost to the boys based on side effects of drastic growth retardation, weight gain, behaviour changes, risk for blood pressure, cataracts, diabetes, osteoporosis. **Proposed change:** Include a fairer judgement on steroids use as standard of care and their benefit (improved heart, ambulation time, less scoliosis, improved lung function) and use within the DMD community. Include also the severe side effects of this treatment when comparing risk/benefit for Duchenne Boys of new therapies against standard of care (and not placebo, as is less often the standard care case).	
123 - 131	2	**Comment:** The special attention here suggests that EMA are expecting rigidity in respect of the very matters about which it was said in 2009 EMA would be flexible. **Proposed change:** To make plain that the objective of the Guidelines is to assist the recent advances in clinical research which have opened up new	Please refer to answers to general comments point 1 – 8.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		perspective for the treatment of DBMD with a clear understanding of the benefit – risk balance.	
123 - 131	11	**Comment:** The special attention here suggests that EMA are expecting rigidity in respect of the very matters about which it was said in 2009 EMA would be flexible. **Proposed change:** To make plain that the objective of the Guidelines is to assist the recent advances in clinical research which have opened up new perspective for the treatment of DBMD with a clear understanding of the benefit – risk balance.	See comment above.
129	12	**Comment:** use of the term “high degree of variability” is inaccurate in this context, based on most recent reports from McDonald et al., where Natural history is defined and clinical meaningful measures based on the 6 minute walk have been established as not variable within the natural history of the boys with Duchenne. **Proposed change:** Refer to the Natural history studies and detail how they could be used as a means to replace placebo arm of a trial where a drug may already have a shown effect and ethical or patient numbers limit placebo use.	**Partly accepted.** The sentence has been moved to the executive summary and the term “high degree of variability” has been amended by “high degree of variability of disease progression”.
132 - 161	2	**Comment:** There is no reference here to papers supporting ethical considerations for clinical trials in conditions affecting children with conditions where	**Not accepted;** this is a regulatory GL and as such in section 3. Legal basis and relevant guidelines, reference is made only to other regulatory documents.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		there is an urgent unmet clinical need or papers in respect of the fast approval options or orphan drugs.	No changes.
132 - 161	11	**Comment:** There is no reference here to papers supporting ethical considerations for clinical trials in conditions affecting children with conditions where there is an urgent unmet clinical need or papers in respect of the fast approval options or orphan drugs.	**Not accepted.** See comment above.
166-168	4	**Comment:** The efficacy of glucocorticoids in slowing the rate of decline in muscle strength and loss of ambulation has been demonstrated in multiple randomized placebo-controlled studies. Corticosteroids are considered as recommended treatment for DMD within the clinical context described in published guidelines (Bushby et al, 2009). We recommend that this status be reflected in the statement. For studies incorporating primary or key secondary endpoints of muscle function, where a stable patient population is required, this would also be internally consistent with the exclusion criteria proposed in section 5.3	**Not accepted** as corticosteroids are not formally approved in Duchenne.
169 – 170	2	**Comment:** These comments appear to contradict the comments at lines 109 – 111. Which is correct?	**Not accepted.** Lines 109-111 refer to the fact that supportive treatments have changed the quality of life and expectancy of DMD patients as compared to decades ago. This is not in contradiction with lines 169 – 172 in which a distinction is made between symptomatic treatment and treatment aiming at disease modification, which may require different study designs, endpoint, etc.
169 – 170	11	**Comment:** These comments appear to contradict the comments at lines 109 – 111. Which is correct?	**Not accepted.** See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
169-172	1	**Comment:** This sentence is not correct at least as far as steroids are concerned, and the sentence should be corrected. There are many different studies that have shown major prolongation of ambulation in DMD treated patients, for a recent reference that summarises the effect of the two most commonly used regimens please refer to Ricotti et al., 2013 (PMID 23250964). **Proposed change:** Please amend sentence to include the following: 'when applying standards of care for DMD, including the two most commonly used steroid regimens, prolongation of ambulation has been achieved (Ref. 6&11: Bushby et al, 2010; Ricotti et al., 2013).	**Not accepted** as corticosteroids are not formally approved in Duchenne and the cited studies are observational studies, representing rather limited evidence of efficacy. Furthermore, the guideline should not be too specific to demanded dosing regimens.
169-172	3	**Comment:** Steroids have been shown to positive effect in the natural history of DMD progression, and thus provide more than just symptomatic support. **Proposed Change:** The sentence should reflect that when using the two most commonly used steroid regimens, prolongation of ambulation has been shown to be improved (Ricotti et al., 2013	**Not accepted**. See comment above.
173	12	**Comment:** "A sustained effect on disability progression needs to be shown" - This line completely misses the potential for use of BioMarkers as surrogates for the indicated benefit effect.	**Not accepted.** A DMD patient would not be interested if there is a signal of dystrophin expression in the muscle biopsy unless he can notice that he is able to do more than before treatment or at least that he is not deteriorating as could be expected. However, the guideline states in section 6 that

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Include what is needed to establish correlation of dystrophin expression with clinical meaningful observations and how natural history can be used to determine baseline measurements. Given current trials show stabilization of boys only after 24 weeks which corresponded to the increase levels of dystrophin, and cross over treated placebo group declined until after this period on the treatment arm, is surely demonstrative of the correlation between dystrophin presence and clinical benefit.	development and validation of biomarkers that could serve as a primary or key secondary endpoint in phase III studies is strongly encouraged.
175-176	1	**Comment:** The use of the term 'delay disease onset' is not correct as the disease onset is from birth. The 'spread of disease' is also misleading, as this implies this is an infectious disease. **Proposed change:** We suggest amending this sentence as follows: 'This includes the delay of symptoms of weakness (or loss of function) in certain muscle groups as well as the delay in time to milestone events'.	**Accepted with slightly modified wording.**
175-176	3	**Comment:** As the onset of DMD is from birth, the concept of 'delay of disease onset' is not really appropriate or accurate. Referring to the progression of disease as 'spread of the disease' is also misleading. **Proposed Change:** Revise the sentence to reflect that this includes the delay of symptoms of weakness, or	**Accepted**. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		loss of function, in certain muscle groups as well as the delay in time to milestone events.	
177 – 178	2	**Comment:** Insisting that a sustained effect on disability progression has to be shown is inflexible and failing in the benefit risk balance. A positive effect on disability progression is surely enough.	**Partly accepted**. Sentence has been slightly modified.
177 – 178	11	**Comment:** Insisting that a sustained effect on disability progression has to be shown is inflexible and failing in the benefit risk balance. A positive effect on disability progression is surely enough.	See comment above.
185-188 & 198-199	5	**Comment:** There are clinical signs that can be predictors of disease (e.g., lying supine, a 5 year old boy with high CK, mild Gowers sign, a patient who can hold his head off table for >20 seconds will be more likely Becker than Duchenne). We acknowledge that alone, clinical signs may not be adequate to specify the diagnosis of BMD from DMD and thereby present prognostic challenges that must be overcome for clinical trials. Hence there is a role for genetic testing. However, we believe that the section on Inclusion criterion (Section 5.2) is problematic in that the adage “genotype confers phenotype” does not always hold up in DMD and BMD. There have been previous studies claiming that out-of-frame or nonsense dystrophin DNA mutations automatically predicted Duchenne phenotype. This has not been fully upheld in the clinical trials experience to date and is a risky approach when conducting trials in small populations of patients. There are also indications in human trials of DMD and BMD, in pre-Ataluren exposed muscle biopsies, of +dystrophin immunoreactivity (presumably revertants). It has been described that Becker and Duchenne can co-exist within the same	**Not accepted**. The cited reference is from 1977 while more knowledge has accumulated thereafter. The in-frame theory of Monaco is still considered valid and confirmed by genetic testing and correlation to clinical presentation in many Duchenne and Becker patients. It is agreed that the definition of the severity generally should rely on a combination of genetic testing and clinical examination. However, for inclusion in mutation-specific studies, genetic testing is a precondition. No changes.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		pedigree with presumably the same dystrophin mutation (Furukawa T, Peter JB. X-linked muscular dystrophy. Ann Neurol 2:414-416, 1977). Therefore, it is our position that there is a role for clinical signs (e.g., age of loss of independent ambulation) to be considered as a part of the inclusion criterion for participation in clinical trials and this should be clarified in the guideline. **Proposed change:** Patients to be included in the clinical studies should have a clinical ~~confirmed~~ diagnosis which is supported by ~~through~~ genetic testing according to state of the art methods. This is particularly necessary for inclusion in mutation-specific therapy studies. Genetic testing will also ensure that subjects with some other forms of muscular disease are not included into the studies which may compromise the homogeneity of the study population (in terms of diagnosis) and may also lead to possibly unnecessary exposure to a drug which is not appropriate for other conditions.	
191-193	1	**Comment:** We propose to change the end of this sentence as below. **Proposed change:** A muscle biopsy could provide complementary information, and improve the diagnostic accuracy.	**Not accepted**, this information is already provided in this section. Moreover, as stated in this section, for medicinal products targeting certain type of genetic defects genetic testing is always an essential prerequisite.
191-193	3	**Comment:** We agree that in the majority of cases the genetic defect can be detected, however as previously noted having a confirmatory muscle biopsy that demonstrates dystrophin expression can improve diagnostic accuracy.	**Not accepted**. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed Change: Add that a muscle biopsy can provide complimentary information and improve diagnostic accuracy.	
198	12	**Comment:** Given the different mutations involved in DMD that are amenable to exon skipping, and the low number of patients with some of these mutations, individual clinical trials with placebo arms would be rendered impossible. Given a defined natural history and an approved surrogate marker for clinical benefit in dystrophin, then trials involving a platform therapy approach could be run together, with outcome measures being that of the level of dystrophin found. Currently this paragraph appears to rule out such a trial given the underlying mutation being different. Without such a platform approach, development of trials in a linear fashion for well over 100 potential exon skipping requirements, would be impossible and unethical should current therapies for exon 51 skipping receive approval. **Proposed change:** Facilitate inclusion of platform based therapy approach based on common surrogate marker of clinical benefit or some means to facilitate a platform approach to therapy development where the drug backbone is common and only the mutation specific antisense is the varying part. The specific targeting actions of the antisense (given it's length) are sufficient to reduce the risk of off target	**Partly accepted**. The low number of patients and the challenge of performing placebo controlled studies has been considered in section 7.5.1, choice of control group.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		effects.	
210-215	3	**Comment:** With the heterogeneity and variability in DMD patients, in conjunction with the use of 6MWT for ambulant boys, it is difficult to study all subsets of boys in a single study as they require different sets of endpoints. Also, for ambulant boys, use of the 6MWT with a cut-off of >230 meters or more, generally precludes starting studies with the older boys. **Proposed change:** Add a sentence that identifies that in DMD, due to the variability and heterogeneity it is not always feasible to include ambulant, transitional and non-ambulant boys in the same studies. Use of the 6MWT as a primary endpoint may preclude focusing on starting studies in older boys, who may meet the 6MWT requirements, and then proceeding with a traditional step-down approach.	**Not accepted**. To study different subgroups of patients in one study is only one option. The paragraph has been amended as follows: *"Depending on the objective of the study, different subgroups of patients with respect to the stage of the disease (ambulant and non-ambulant), functional status and developmental stage (e.g. child of pre-school age vs. schoolchild) should be selected a priori. In general, the patient population which is rather limited in numbers should cover a broad range, if possible; normally (but not in all cases) studies should start in older children with a step-down approach. If an effect in specific stages of the disease is expected according to the mechanism of action of the product (e.g. compound acting on fibrotic tissue in muscles), then an alternative approach may be considered. Extrapolation should be discussed in light of potential clinical benefit in other stages of disease, and also in light of potential concerns with regard to safety or dosing for different age groups."*
210	12	**Comment:** In a scenario where a single therapy reduces the disease from DMD to a BMD like phenotype (i.e. exon skipping), alternate therapies will need to be included in a cocktail approach to for instance boost muscle or protect the cell membrane as well as increasing a shortened dystrophin. In this case, how will DMD and BMD boys be distinguished? Natural BMD versus therapy induced BMD ?	**Not accepted.** Since the GL is prepared to provide guidance on general principles in the development of any medicinal products for the treatment in DMD (symptomatic, disease modifying) a balance between not being too specific and providing some general principle requirements is sought. However, companies are invited to discuss these issues by scientific advice.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Included details about how DMD boys who with treatment now have BMD phenotypes and how this then relates to originally diagnosed BMD patients. In these instances, are both allowed in the same trial for additional therapies, for instance a muscle inhibitor antagonist?	
212-217	1	**Comment:** The comment that studies should start in older children with a step-down approach should be amended. Therapies that specifically target muscle would only demonstrate a positive outcome in patients who still have muscle. As the disease progresses and muscle is lost this would indicate that younger patients would show greater benefit from these therapies than older patients. However, therapies that target fibrosis may have a clear benefit in older patients who have already lost most if not all their muscle, which at that stage will have been replaced by fibrotic tissue.	**Accepted;** "but not in all cases" has been included.
212 – 215	2	**Comment:** Emphasis here surely needs to be placed upon the fact that the patient population is very small. Therefore, the degree of flexibility should be made clearer.	**Accepted**. See comment above.
212 – 215	11	**Comment:** Emphasis here surely needs to be placed upon the fact that the patient population is very small. Therefore, the degree of flexibility should be made clearer.	**Accepted**. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
213-214	4	**Comment:** The suggestion that "normally studies should start in older children with a step-down approach" should be re-considered or expanded to consider all the relevant factors. This is a rare population that does not always progress at a very high rate. For these reasons, with drugs aimed at inhibiting disease progression it may only be practical to study a population that is rapidly progressing in disease severity and for which there is an available endpoint, such as the six minute walk test or North Star Ambulatory Assessment (NSAA). This will necessarily direct development to specific age groups, which might be younger. Alternatively, evaluation of a drug to slow cardiac or respiratory decline may require an older patient group. In addition, disease-modifying therapies, such as anti-inflammatory or muscle building agents, are likely to be more efficacious when used in younger and less severely affected children than in patients with extensive fibrosis and loss of muscle mass. In the end, the risk/benefit profile for each potential study population will have to be considered taking into account the huge unmet need and the practical issues faced by drug developers in this indication.	**Accepted.** The paragraph has been amended as stated above.
216-219	4	**Comment:** The statement suggests that motor function interventions be evaluated sequentially in older ambulant patients, and then in non-ambulant boys. The statement is limiting. The ambulant population spans an extended age range with a mechanism of disease that is identical in older and younger boys. Therefore, if efficacy is demonstrated in the older subset of the ambulant population, based on an endpoint such as 6-minute-walk distance, it can be justified to subsequently extend investigation to the younger ambulant	**Comment accepted.** Please refer to the comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		population for whom this endpoint is not easily measured, for example due to inability to take directions. By using clinical demonstration of safety, PK and extrapolation of efficacy from the older ambulant population, the younger population could be evaluated. It is not appropriate that investigation in the younger ambulant population is contingent on prior completion of studies in a non-ambulatory population.	
223-227	**5**	**Comment:** Regarding the progressive disease character, we do not consider that different cut-off scores for an appropriate scale should be used to include patients with a certain degree of severity to assure sensitivity to change. Appropriate, validated scales may be useful to measure longitudinal treatment differences, however, utilizing a particular cut-off score for inclusion may inadvertently introduce bias. There are more reliable criteria based on natural history data that can be predictive of disease progression. Clinically meaningful benefit may be measured at all stages of the disease. **Proposed change:** ~~Regarding the progressive disease character, different cut-off scores for an appropriate scale should be used to include patients with a certain degree of severity to assure sensitivity to change. Thresholds for clinical severity of motor function impairment, respiratory and cardiac symptoms, associated cognitive deficits as well as further relevant co-morbid symptoms should be defined. However, at present only few assessment tools are adequately validated. (See also section 6).~~	**Not accepted**. The use of certain cut-off points is necessary to ensure some homogeneity of the study population and hence higher chance for sensitivity to change. It is agreed that new therapies should be developed aiming at a clinically meaningful benefit for any stage of the disease, however the benefit and hence treatment goals can be very different at different stages. Therefore the same primary endpoint cannot be used for the entire patient population. **Outcome:** The proposal to remove the sentence is not endorsed; it has been kept with slightly modified wording: "*With due consideration of the progressive nature of the disease, different cut-off scores for an appropriate scale should be used to assure sensitivity to change. Thresholds for clinical severity of motor function impairment, respiratory and cardiac symptoms, associated cognitive deficits, as well as further relevant co-morbid symptoms should be defined a priori.*"
226-227	1	**Comment:** we suggest deleting the last sentence of the paragraph, as many of the proposed assessment tools for muscle function have been validated and published over the last couple of years, as was	**Accepted**, the last sentence has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		presented at the TREAT-NMD workshop in London (http://www.treat-nmd.eu/industry/regulatory-affairs/dmd-workshop-2013/).	
230-231	1	**Comment:** This might depend on the nature of a study. In a phase 1a or 1b study in which function is not an issue, why would one exclude a child started with steroids 4 months earlier? **Proposed change:** This sentence should be specified 'for efficacy assessment'.	**Partly accepted.** The criteria as presented in the GL are based on clinical experience and literature about treatment with corticosteroids. The proposal to shorten the times is not based on evidence that 3 months since corticosteroid initiation is sufficient to achieve a steady state, neither that 1 month on concomitant medication is sufficient. It is based on practical arguments related to limited availability of patients. However, since both corticosteroids and any other concomitant medication may have an effect on muscle function, but also heart and lung function, and all these have an impact on the performance of the 6MWT, it is accepted that concomitant medication should be stable in clinical studies. The experience so far with clinical studies in DMD has shown that this was implemented in the study protocols. Therefore it is proposed not to reduce the times as proposed, since this may jeopardize study results and their interpretation, which is not in the interest of development of medicinal products for the disease. If in the future scientific evidence emerges that the proposed shorter times are sufficient to achieve stabilization, a revision of the GL may be considered. However, a statement that this is for efficacy assessment will be included.
230-231	3	**Comment:** This exclusion may depend on the nature of the study. In earlier studies, e.g. phase 1a or 1b, it	**Partly accepted.** See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		may not be necessary to exclude boys started on steroids within 4 months. **Proposed change:** Add sentence that in early phase studies this exclusion criterion might not be necessary.	
230 – 231	2	**Comment:** At lines 216 to 217, it is recommended that studies should be started in ambulant males. Children with DMD stop walking by the age of 12. Children also generally start to take Corticosteroid therapy from very early and usually by the ages of 5 or 7 years old with the dose changing depending on the child's increasing weight. Therefore, on the one hand the Guidelines state that studies should be conducted in ambulant boys but then if there have been changes in corticosteroid use, the patient should be excluded. We have a small heterogeneous patient population in any event. They take steroids to keep walking longer and to qualify for trials but that very use then excludes them from trials. This is the reality of the situation and why there is a need for flexibility and understanding.	**Not accepted.** Lines 230-231 do not aim at excluding patients from clinical studies, but ensuring some stability in the treatment regimen. The criteria as presented in the GL are based on clinical experience and literature about treatment with corticosteroids. Since both corticosteroids and any other concomitant medication may have an effect on muscle function, but also heart and lung function, and all these have an impact on the performance of the 6MWT, it is accepted that concomitant medication should be stable in clinical studies. The experience so far with clinical studies in DMD has shown that this was implemented in the study protocols. There is flexibility and understanding about the need for corticosteroid treatment. The authors of this comment admit themselves that corticosteroid have an effect on DMD boys performance. Therefore for the purposes of a clinical study including patients without any criteria for corticosteroids is not the best way to go, since this may jeopardize study results and their interpretation. This is not in the interest of development of medicinal products for the disease. If in the future scientific evidence emerges that shorter times are sufficient to achieve stabilization, a revision of the GL may be considered.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
230-231-232	9	**Comment:** Lines 230-231-232 indicate two exclusion criteria: initiation of systemic corticosteroid therapy within 6 months or changes in dosing within 3 months prior screening; any change in relevant concomitant therapies within 3 months prior to start of study treatment. **Proposed change:** We believe that these criteria are too rigid, and may limit the availability of patients, which are already difficult to find. We suggest to change 6 months into 3 months, and 3 months into 1 month. These intervals are sufficient to guarantee a stabilization of steroids effects.	**Not accepted**. See comment above.
230 – 231	11	**Comment:** At lines 216 to 217, it is recommended that studies should be started in ambulant males. Children with DMD stop walking by the age of 12. Children also generally start to take Corticosteroid therapy from very early and usually by the ages of 5 or 7 years old with the dose changing depending on the child's increasing weight. Therefore, on the one hand the Guidelines state that studies should be conducted in ambulant boys but then if there have been changes in corticosteroid use, the patient should be excluded. We have a small heterogeneous patient population in any event. They take steroids to keep walking longer and to qualify for trials but that very use then excludes them from trials. This is the reality of the situation and why there is a need for flexibility and understanding.	**Not accepted**. See comment above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
237-238	1	**Comment:** This should be for treatments that are not mutation-specific. **Proposed change:** subjects without a confirmed mutation in the dystrophin gene or a muscle biopsy confirming DMD; subjects with another neuromuscular disease.	**Not accepted** as for mutation-specific therapy studies the confirmed mutation is considered essential.
242 – 269	2	**Comment:** The general comments with regard to biomarkers or surrogate end points as a primary end point made in the general points above are repeated here. Further, regard needs to be had to quality of life (or ADL) as a primary endpoint given the severe consequences of the condition.	**Not agreed;** the importance of ADL and quality of life endpoints is recognised since the final outcome of any treatment should aim at improving the patient's clinical well-being. However a recommendation to consider such endpoint as primary will not be given in this guideline. The reason is that these measures are too variable and a detectable difference may require too large sample sizes if this is chosen as a primary endpoint is a clinical study. However in case a sponsor would like to pursue this path, this may be discussed a priori in the form a scientific advice.
242 – 269	11	**Comment:** The general comments with regard to biomarkers or surrogate end points as a primary end point made in the general points above are repeated here. Further, regard needs to be had to quality of life (or ADL) as a primary endpoint given the severe consequences of the condition.	**Not accepted.** See comment above.
245 - 258	**5**	**Comment:** The draft guideline indicates that muscle strength should be a co-primary endpoint with motor function. However, muscle strength decline is gradual and is expected to be less sensitive than motor	**Partly accepted**. It is agreed that most publications on natural course indicate that muscle strength improvement is less sensitive to change than motor function. The request to focus clinical studies only on the 6MWT as single primary

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		function to improvement following treatment[1,2]. Improvements in motor function such as 6 MW can be clinically significant with no significant changes to muscle strength. Function is more important to patients than strength, with the 6MWD being a validated clinically meaningful endpoint of function. Earlier functional abilities are known to predict later functional abilities and timing of loss of clinically meaningful functions (milestones) predict when later milestones will be lost. Clinically significant changes in motor function are expected to be observed in the typical 48 week duration of double blind trials, which is unlikely to be the case with muscle strength[1,3-5]. Muscle strength improvement may only be seen, if any, after at least 2 years of treatment. It is therefore proposed that muscle strength could be included as a secondary endpoint rather than as a co-primary endpoint and we consider that a single motor functioning endpoint such as 6MWD is appropriate as a primary endpoint. In addition, statistical power will be compromised by co-primary endpoints, particularly where one is more relevant and involves a very small disease patient populations. **Proposed change:** "Functional mobility is considered as the most relevant outcome measure for patients affected by DMD and BMD. Treatment effects on functionality should be backed up by effects in the activities of daily living (ADL). The primary pathophysiological effect of DBMD is a decline in muscle strength and motor function and these are therefore important parameters to measure. Muscle strength and motor function are closely related but quite distinct motor system parameters. Many additional factors other than muscle strength may influence the ability to walk[13]. In addition, clinically relevant improvements in patient's motor function	endpoint is not accepted since a maintenance of a certain level of muscle strength (hence no further deterioration) is considered an important achievement in this disease and will be considered as supportive evidence for efficacy. Therefore two endpoints should be selected from the domains muscle strength and motor function. However, the paragraph has been revised; only one primary endpoint is requested (note: several of the cited articles were sponsored by ataluren company).

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		following treatment may be observed with little, or no, improvement in muscle strength. ~~Therefore, to provide evidence for a clinically relevant effect, a demonstrated effect on muscle strength always needs to be translated into parameters of motor function, or vice versa.~~ ~~Two co-~~The primary ~~endpoints~~ endpoint should therefore be pre-specified from the ~~domains~~ motor functioning domain ~~and muscle strength~~. Depending on the treatment goals, measures of cardiac or respiratory function, e.g. in DMD-associated dilated cardiomyopathy, could also be selected as relevant primary endpoints. Secondary outcome measures should include change from baseline in muscle strength, activities of daily living (ADL), respiratory and cardiac function…. Results for the ~~co-~~primary outcome measure~~s~~ and the most important secondary endpoints should be discussed both in terms of clinical relevance and statistical significance……." References 1) McDonald CM, Henricson EK, Abresch RT, Florence JM, Eagle M, Gappmaier E, Glanzman AM; PTC124-GD-007-DMD Study Group, Spiegel R, Barth J, Elfring G, Reha A, Peltz S. THE 6-minute walk test and other endpoints in Duchenne muscular dystrophy: Longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve. 2013 May 16. 2) Beenakker EA, Maurits NM, Fock JM, Brouwer OF, van der Hoeven JH. Functional ability and muscle force in healthy children and ambulant Duchenne muscular	

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		dystrophy patients. Eur J Paediatr Neurol. 2005;9(6):387-93. 3) Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, McDonald CM. The 6-minute walk test and person-reported outcomes in boys with duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. PLoS Curr. 2013 Jul 8;5. 4) Mazzone ES, Pane M, Sormani MP, Scalise R, Berardinelli A, Messina S, Torrente Y, D'Amico A, Doglio L, Viggiano E, D'Ambrosio P, Cavallaro F, Frosini S, Bello L, Bonfiglio S, De Sanctis R, Rolle E, Bianco F, Magri F, Rossi F, Vasco G, Vita G, Motta MC, Donati MA, Sacchini M, Mongini T, Pini A, Battini R, Pegoraro E, Previtali S, Napolitano S, Bruno C, Politano L, Comi GP, Bertini E, Mercuri E. 24 month longitudinal data in ambulant boys with Duchenne muscular dystrophy. PLoS One. 2013;8(1):e52512. 5) Mazzone E, Vasco G, Sormani MP, Torrente Y, Berardinelli A, Messina S, D'Amico A, Doglio L, Politano L, Cavallaro F, Frosini S, Bello L, Bonfiglio S, Zucchini E, De Sanctis R, Scutifero M, Bianco F, Rossi F, Motta MC, Sacco A, Donati MA, Mongini T, Pini A, Battini R, Pegoraro E, Pane M, Gasperini S, Previtali S, Napolitano S, Martinelli D, Bruno C, Vita G, Comi G, Bertini E, Mercuri E. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology. 2011 Jul 19;77(3):250-6	
248-256	7	**Proposed change: *6.1. Efficacy variables*** The primary pathophysiological effect of DBMD is a decline in muscle strength and motor function and these are therefore important parameters to measure. Muscle strength and motor function are closely related	**Accepted**. Text has been revised.

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		but quite distinct motor system parameters. Many additional factors other than muscle strength may influence the ability to walk [13]. Therefore, to provide evidence for a clinically relevant effect, a demonstrated effect on muscle strength always needs to be translated into parameters of motor function, or vice versa. Two ~~co-primary~~ endpoints should ~~therefore~~ be pre-specified from the domains motor functioning and muscle strength one should be as primary endpoint and the other as secondary endpoints. Depending on the treatment goals, measures of cardiac or respiratory function, e.g. in DMD-associated dilated cardiomyopathy, could also be selected as relevant primary endpoints.	
249-253	3	**Comment:** We agree that muscle function and strength are both important and that they are closely related. However it is important to note they are also distinct and are not linearly related in ambulant or non-ambulant boys. For example it has been demonstrated that in early stages of disease symptomology, boys lose much more strength than function. Later in the disease progression they lose little strength and function declines rapidly. For therapies that target restoration of dystrophin, it is unlikely to see improvement in strength, but rather that the increased production of dystrophin helps protect muscles from further damage, which will translate into functional improvement. It might be more appropriate to expect to see improved function also correlate with other secondary outcome measurements (e.g. changes in ADL, health-related	**Partly accepted**. It is agreed that most publications on natural course indicate that muscle strength improvement is less sensitive to change than motor function. However, the request to focus clinical studies only on the assessment of motor function is not accepted as maintenance of a certain level of muscle strength (hence no further deterioration) is considered an important achievement in this disease and will be considered as supportive evidence for efficacy. Therefore we consider to request one of these endpoints to be used as primary endpoint and the other as secondary endpoint, meaning no statistical significance is requested for the secondary endpoint. The sentence has been rephrased: "*Although it is well known and recognised that there is no linear correlation between muscle strength and function in boys with DMD, for total evidence of clinical efficacy an effect*

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		quality of life and caregivers surveys, etc.) **Proposed change:** Modify the wording to acknowledge that, depending on the therapeutic target, it may not always be necessary or possible to always translate effect of function or strength on the other.	*on motor function should be supported by an effect on muscle strength. In addition, treatment effects on functionality should be backed up by effects in the activities of daily living (ADL). Similarly, a compound aiming at increasing or maintaining muscle mass should show in addition to efficacy on muscle strength also an effect (or at least no detrimental effect) on function to evaluate the clinical relevance."*
251-253	1	**Comment:** Evidence for a clinically relevant effect should be demonstrated in strength and translated into parameters of function, and vice versa. We do not agree. As demonstrated in recent publications and reported at the TREAT-NMD workshop in London, there is no linear correlation between muscle strength and function in boys with DMD (McDonald et al., Muscle & Nerve, pp357-368, 2013). It therefore seems to be unreasonable to always ask for evidence that there is a clear correlation between strength and function. Please also see the comment below.	**Accepted**; *"translated"* has been deleted. See also comment above.
254-256	1	**Comment:** mentions that co-primary endpoints of strength and function should be used for clinical trials. We do not agree. Strength and function are both important outcomes but are not linearly related. A co-primary would dilute the power of the most relevant measure and would also increase the number of patients required to power a trial. Functional ability measured by motor performance is the most	**Partly accepted.** See comment above. This paragraph has been rephrased as follows: "*Two endpoints should be selected from the domains muscle strength (depending on the functional status and the compound tested) and motor function. According to the motor system parameter estimated to be particularly affected, one*

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		appropriate primary endpoint with other measures which may include strength and timed tests as secondary endpoints (this is based on discussions at a recent ENMC workshop on exon skipping – Aartsma-Rus et al, Neuromuscular Disorders, 2013). The primary endpoint may vary according to the stage of the disease. For example in ambulant boys 6MWT or North Star Ambulatory Assessment (NSAA) may be most appropriate whereas in older non-ambulant boys and men one of a variety of respiratory function tests or upper limb performance may be more appropriate. In infants development scales may be suitable. It has been demonstrated in mouse models that express low dystrophin levels that muscle pathology and motor function is improved and suggest that in patients low levels of dystrophin may benefit functionally, while strength is not improved (van Putten et al., 2013; van Putten et al., 2012). Furthermore, extensive data is now available showing that the correlation between strength and function is not linear in ambulant patients (McDonald et al., Muscle & Nerve, pp357-368, 2013). In fact, at early stages, patients lose a lot of strength, while decline in function is slow. By contrast at late stages patients lose a little strength and function declines rapidly. Finally, in studies restoring dystrophin, it is unlikely to improve strength, as dystrophin does not make muscle fibres stronger, but protects them from damage during contraction. Thus it is anticipated for compounds restoring dystrophin that the decline in strength will be	*should be selected as primary endpoint and the other as secondary endpoint. Effects on the single selected primary endpoint should be supported by results from the most relevant secondary endpoints for consistency. Considering the relatively small number of patients in such studies in this context reference is also made to the Guideline for Small Populations. Depending on the treatment goals, e.g. in DMD-associated dilated cardiomyopathy effects on cardiac or respiratory function measured with relevant tools, could also be selected as relevant primary endpoints."*

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		slower, but not that muscles will become stronger. Taken together, asking for co-primary endpoints will dilute the effect, requiring larger groups of patients to find significance for both endpoints and given the non-linear correlation between strength and function it is unlikely that significant findings will be found for both. **Proposed change:** Replace the suggestion of co-primary outcomes by a primary endpoint for muscle function, backed up by secondary endpoints for additional muscle function tests and/or strength (depending on the age group and the compound tested).	
254-256	3	**Comment:** The guidance suggests requiring two co-primary endpoints from the domain of motor function and muscle strength. We disagree with this suggested requirement. As noted in the previous comment, strength and function, while both being important outcomes, are not related in time. In DMD it would be anticipated that a treatment effect would improve muscle function long before an increase in muscle strength could be observed. This due to the nature of the muscle pathology that characterises this disease. At the level of the individual muscle fibre there is severe disorganisation including costameric derangement and abnormal orientation of sarcomeres; at the level of the fibre bundle there is splitting, fibrosis and aberrant innervation. Complex and time-consuming regeneration processes are required to	**Partly accepted**. See comment above.

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		restore muscle strength whereas function can be stabilized or restored more quickly and it is more meaningful for clinical function such as ambulation. Moreover function is more relevant for maintenance of activities of daily living. Walking is not performed through strength, playing the piano is not accomplished by strength. For both a minimum threshold of strength is required but most of all, appropriate function is needed. Improving strength without simultaneous improvement of function can be dangerous for muscle (eg myostatin deficient cattle drop dead when chased). Evidence of the different sensitivity to change of these two endpoints comes from the PCT07 ataluren trial. In this study, the minimal clinically important difference was 15.7 – 17.9% for knee extensor strength compared with 8 – 8.9% for the 6 MWD (McDonald et al. Muscle & Nerve 2013 May 14. doi: 10.1002/mus.23905). Moreover in the placebo arm (n=57), there was no significant differences in strength change over 48 weeks for corticosteroid treated versus non corticosteroid treated patients Requiring two co-primaries to be pre-specified would unnecessarily increase the burden of proof to demonstrate efficacy, if both were required to show a significant treatment effect. Accounting for multiplicity would increase the required number of patients. We suggest that functional ability that is measured by motor performance (e.g., 6MWT for ambulant boys) is the most appropriate endpoint, which can then be	

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		supported by other appropriate secondary outcome measurements such as the NSAA. We agree that the primary endpoint may vary depending on the treatment goals and the stage of the disease. Regardless, we agree that the results of the single primary outcome measure and the supporting secondary measurements should be discussed both in terms of clinical relevance and statistical significance. **Proposed change:** We would suggest to replace the suggestion of a co-primary endpoint with a single primary endpoint for muscle function relevant for the study population (e.g., 6MWT in ambulant boys) and that the primary would be supported by other secondary measures as noted in the guidance.	
254-256	4	**Comment:** We ask that the concept of requiring co-primary endpoints be re-considered based on both practical and clinical considerations. Regarding practical considerations, study design in this area is difficult enough given the rare nature of the disease and uncertainty over normative standards, as well as the considerable shortcomings of currently available assessment tools, which are acknowledged in section 6.2. Requiring that two primary endpoints be successful to have an approvable product will make drug development even more difficult and could delay or forestall the approval of clinically meaningful therapies. Further, requirement of a co-primary would dilute the power of the most relevant, clinically meaningful endpoint and would likely significantly increase the number of patients required to appropriately power the clinical trial.	**Partly accepted**. See comment above.

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		The following example illustrates the issue. Imagine that a drug substantially improves mobility, or upper body motor function in such as way that activities of daily living are substantially improved, but for some reason does not improve isolated measures of muscle strength. In Pfizer's opinion it would not be a medically appropriate regulatory decision to not approve this product based on the trial having failed a co-primary endpoint that is less clinically meaningful than the co-primary endpoint that was met. Instead, in Pfizer's view, a better strategy would be to utilize a clinically meaningful single primary endpoint (if one exists), rather than requiring the use of co-primary endpoints. The actual tests may vary at different stages of disease with 6MWT and NSAA appropriate for ambulatory patients and upper limb performance or respiratory tests more appropriate for non-ambulant, older boys. This perspective is supported by text in section 6.1 of the guideline; "Functional mobility is considered as the most relevant outcome measure for patients affected by DMD and BMD. Treatment effects on functionality should be backed up by effects in the activities of daily living (ADL)."	
254-255	6	**Comment:** The draft guidelines recommend that "Two co-primary endpoints should therefore be pre-specified from the domains motor functioning and muscle strength." The relationship between quantitative knee extension strength and walking function (walking velocity or 6MWD) is logarithmic (Abresch 2011; McDonald 2013a). Thus, depending on the stage of the disease there is dissociation between strength and function. Typically from 4 to 7 years a large change in strength is associated with a small change in function.	See comment above.

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		After the age of 7-8 years a large change in function is associated with a small change in function (Abresch 2011; McDonald London presentation 21 June 2013; McDonald 2013b). Data from the Cooperative International Neuromuscular Research Group confirms that a loss of meaningful milestones is predicted by loss of a critical threshold of antigravity strength determined by MMT. This small change in quantitative strength often occurs with loss of antigravity strength by manual muscle testing and impacts the ability of DMD patients to compensate to maintain function. Strength may be appropriate for therapeutics leading to short-term benefit in terms of increased force production of fibers. Strength is not appropriate for clinical trials of therapeutics that stabilize functional loss without changing strength (e.g. dystrophin restoration). Placebo data from the ataluren trial (McDonald 2013b) indicate decline in knee extension strength was minimal over 48-weeks (< the MCID). Thus a statistically significant increase in strength would likely need to be shown for there to be a significant drug effect. Function is always more important to patients and families as compared to strength. Specific mechanisms of action do not lend themselves to strength and function as co-primary endpoints (e.g. dystrophin restoration). Most importantly statistical power will be compromised by the use of co-primary endpoints particularly when one (function) is more responsive to therapy and more meaningful to patients than the other (strength).	

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		Proposed change: Remove the recommendation that 'two co-primary endpoints should therefore be pre-specified from the domains motor functioning and muscle strength."	
254-255	8	**Comment:** "Two co-primary endpoints should therefore be pre-specified from the domains motor functioning and muscle strength. " Two co-primary endpoints will dilute the power of the most relevant measure and will also increase the number of patients required to fully power a trial. This would be particularly demanding in an orphan disease with limited number of patients available. Muscle function and strength have been shown to be highly correlated, however such a correlation is not linear but logarithmic (C. McDonald et al, 2013). In younger children a rapid decrease in muscle strength is observed with relatively small changes in function, while in older ones the opposite occurs (C. McDonald et al, 2013). Therefore the use of strength and function as co-primary at the same time would mean assessing parameters with very different sensitivity and possibility to change. As such the need to power the study for the least sensitive parameter would call for a large sample size. **Proposed change:** Function or strength should be the	**Accepted**. See comment above.

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		pre-specified primary endpoint. The parameter which has not been selected as primary endpoint should be assessed as secondary endpoint.	
254	12	**Comment:** Primary outcome measures does not include surrogate markers of clinical benefit. **Proposed change:** Surrogate markers for dystrophin production and other markers that have been validates should be facilitated as options for endpoints. This is critical for biomarkers such as MRI, which will reduce invasive muscle biopsies for the kids.	**Partly Accepted**. Section 6.2 already states that at this stage there is no suitable biomarker that could be a primary or key secondary endpoint in phase III studies, but development of such biomarkers is encouraged. MRI measures have been implemented as their use as exploratory or secondary endpoints is encouraged for generating additional data.
257-258	5	**Comment:** There is an inconsistency in the guideline in that in lines 360 to 365 it states that the use neuropsychological tests in DMD and BMD are considered exploratory, however, in line 257 it states that cognitive ability should be included as a secondary outcome measure. We do not consider that secondary outcome measures within relatively short term clinical trials should also include 'cognitive ability' because as stated in the guideline, experience of neuropsychological tests in DMD/BMD patients within clinical trials is limited and their use is still considered exploratory. **Proposed change:** Secondary outcome measures should include change from baseline in activities of daily living (ADL), respiratory and cardiac function~~, cognitive ability~~, health-related quality of life and caregivers survey.	**Partly accepted**. Change in cognition can be measured within 1 year study (such is the experience with studies in some psychiatric conditions). However it is agreed that there is little experience in DMD. Outcome: Cognitive ability will be advised as an exploratory endpoint.
259 – 260	2	**Comment:** There are many more ADL end points that exist. For example, a non-ambulant boy may	**Not accepted.** The importance of ADL and quality of life endpoints is recognised (see also above). However a

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		experience a significantly enhanced quality of life because he is able to twiddle his fingers (and so use a motorised wheelchair) in the way that he could not previously do! **Proposed change:** Consider quality of life/ADL as a primary endpoint given the severe consequences of the condition.	recommendation to consider such endpoint as primary will not be given in this guideline. The reason is that these measures are too variable and a detectable difference may require too large sample size if this is chosen as a primary endpoint in a clinical study. This may not be feasible. However if a sponsor would like to pursue this path, this may be discussed a priori in the form a scientific advice.
259 – 260	11	**Comment:** There are many more ADL end points that exist. For example, a non-ambulant boy may experience a significantly enhanced quality of life because he is able to twiddle his fingers (and so use a motorised wheelchair) in the way that he could not previously do! **Proposed change:** Consider quality of life/ADL as a primary endpoint given the severe consequences of the condition.	**Not accepted.** See comment above.
265-269	4	**Comment:** We agree with the concept of using a responder analysis to serve as supportive evidence for a clinically meaningful effect. However, we recommend that the final guideline reflect clearly that this is a supportive element, as responder analyses involve dichotomous endpoints, which are inherently less sensitive than continuous endpoints. In a rare population, it is important that primary analyses utilize all available data, such as occurs with the use of continuous endpoints.	**Not accepted.** See comment below.
266 to 269	5	**Comment:** We agree that if a 'responder' can be defined and validated, it can give a more clinically	**Not accepted**. In fact the definition of responder is according to a pre-specified level of achievement on a certain endpoint.

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		meaningful endpoint. Alternatively, if a validated definition of responder is unavailable, when there is a recognised minimal clinically important difference (MCID) results can be discussed in the context of this MCID. **Proposed change:** In order to support an estimate of clinical relevance, results should also be expressed in terms of the proportion of responders where possible. Definition of responders and/or disease progression should be based on clinical considerations and be specified prospectively in the clinical study protocol. If a validated definition of a responder is not possible, when there is a recognised minimal clinically important difference (MCID), results can be discussed in the context of this MCID.	If this will be the MCID or a certain percent difference in change from baseline on the primary endpoint is the same. Therefore the comment is not fully understood and also why and in which situations a responder cannot be defined. Outcome: The proposed changes are not adopted.
270 – 283	2	**Comment:** It is stated that no specific recommendation is made to the choice of measurement tools but then question marks are raised about the measurement tools that are currently being used in clinical trial studies. That is grossly unhelpful and is not a guideline. It should be made plain that these are recognised methods of measurement and when coupled with the self-reporting encouraged at lines 271 to 276, should provide useful information.	**Not accepted**. Please refer to general comments above (point 7).
270 – 283	11	**Comment:** It is stated that no specific recommendation is made to the choice of measurement tools but then question marks are raised about the measurement tools that are currently being used in clinical trial studies. That is grossly unhelpful and is not a guideline. It should be made plain that	**Not accepted**. See comment above.

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		these are recognised methods of measurement and when coupled with the self-reporting encouraged at lines 271 to 276, should provide useful information.	
277-283	1	**Comment:** This paragraph should be amended to reflect the good correlative nature of various outcome measures (such as 6MWT) with later outcomes, on one hand, and also the good correlation between many of these outcome measures, such as 6MWT and NSAA (Mazzone et al., 2011; Mazzone et al., 2013).	**Not accepted**. Since the GL is prepared to provide guidance on general principles in the development of any medicinal products for the treatment in DMD (symptomatic, disease modifying) a balance between not being too specific and providing some general principle requirements is sought.
277-283	3	**Comment:** While it is still correct that it is always clear how some parameters correlate with quality of life, time to death and other life-changing events, there is now adequate and acceptable evidence that shows correlation with some key outcomes (e.g. 6MWT) and subsequent milestones. Also the occurrence of one milestone (e.g., timed events) is related and correlates with other subsequent milestone (e.g., loss of ambulation). Recently in one study (Mazzone et al., 2013) there was a correlation between North Star and the 6MWT and subsequent loss of ambulation within 2 years. **Proposed change:** The paragraph should be amended to reflect the correlation of milestone outcome events that have been described and documented.	**Not accepted**. See comment above.
277-283	4	**Comment:** This comment should reflect that, in general, disease progression in DMD is considered	**Not accepted.** See comment above.

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		sequential and slowing of one stage of disease. For example, the inability to stand from the floor is correlated to later clinically meaningful outcomes such as 6MWT (work of Craig MacDonald). There are several published reports by MacDonald and colleagues, and also Mercurio and colleagues, that have identified significant correlations between a number of measureable outcome endpoints. For example, a recent publication by Mazzone et al (2013) indicates that North Star and 6MWT measures are able to predict loss of ambulation.	
282-283	1	**Comment:** It states that it is not clear how timed activities correlate with quality of life, time to death and other life-changing events (e.g. time to wheelchair). This is not true – there are studies reporting a correlation between timed items and loss of ambulation (McDonald et al, Muscle & Nerve, pp343-356, 2013). In a recent study (Mazzone et al, 2013) the value of the North Star and the 6MWT in predicting loss of ambulation within 2 years has also been reported. **Proposed change:** Revise text based on these new publications.	**Partly accepted**. "*still not clear"* has been revised by "*further data are needed in order to establish how ….*"
291-294	1	**Comment:** We propose to change the text of this paragraph – see below. **Proposed change:** "Generic scales with such a wide scope will include items that are not specific to the disease and severity of a target population so may not	**Partly accepted**. The sentences has been rephrased as follows: "*For both ambulant and non-ambulant patients, the Motor Function Scale (MFM) is a 32-item validated global scale for children from 6 years of age with neuromuscular disorders including DMD. It offers a continuous assessment regardless*

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		be sensitive or specific enough for use in a clinical trial. However the MFM could be appropriate for studies which have a wide range of diseases and different severities."	*of disease severity and ambulatory status, thus ……."*
291-296	3	**Comment:** We agree that the MFM is a validated global scale and could be appropriate for studies which have a wide range of neuromuscular disorders. However some generic scales may not be sensitive or specific enough for use in clinical trials, as they include items that are not specific to the disease and severity of the target population. NSAA, being disease and stage specific to ambulatory DMD boys, has essentially replaced the HMAS in clinical trial settings. Further the NSAA provides a linearized score which is related to activities of daily life for boys with DMD. **Proposed change:** The guideline should be revised according to the above comments.	**Accepted**. Non-specific NSAA has been replaced by disease-specific North Star Ambulatory Assessment (NSAA)
295-297	1	**Comment:** We propose to change the text of this paragraph –see below. **Proposed change:** "The NSAA is disease and stage specific to ambulatory DMD and has replaced the HMAS in both clinical and trial settings. NSAA offers a robust linearized score which is meaningfully related to activities of daily life for DMD. Responsiveness has been demonstrated in relationship to steroid regime and a minimal important difference (MID) has been	**Partly accepted**. Non-specific NSAA has been replaced by disease-specific North Star Ambulatory Assessment (NSAA). However, as stated above since the GL is prepared to provide guidance on general principles in the development of any medicinal products for the treatment in DMD (symptomatic, disease modifying) a balance between not being too specific and providing some general principle requirements is sought.

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		published (Mayhew et al., 2013). A positive correlation exists between the NSAA and the 6MWT (Mazzone et al., 2012) and NSAA has been adopted as a secondary outcome measure in several therapeutic trials." Please refer to the following relevant references: Mazzone (PMID 19553120), Mazzone (PMID 20634072), Mayhew (PMID 21410696), Mazzone (PMID 21734183), Scott (PMID 21954141), Ergul (PMID 22404693), Mazzone (PMID 23326337) Detecting meaningful change in North Star Ambulatory Assessment in Duchenne Muscular Dystrophy. Anna G. Mayhew, Stefan J. Cano, Elaine Scott, Michelle Eagle, Kate Bushby, Adnan Manzur, Francesco Muntoni, ON BEHALF OF THE NORTH STAR CLINICAL NETWORK FOR PAEDIATRIC NEUROMUSCULAR DISEASE. DMCN, 2013	
295-297	4	**Comment**: This comment should reflect current status. The North Star Ambulatory Assessment should be considered as a highly appropriate and robust measure for evaluation of function in the ambulatory DMD population, as young as 3.5 yrs. The NSAA has been found to relate to important activities of daily living and correlates well to the 6MWT (Mazzone et al., 2012). Mazzone (PMID 19553120), Mazzone (PMID 20634072), Mayhew (PMID 21410696), Mazzone	**Partly accepted.** See comment above.

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		(PMID 21734183), Scott (PMID 21954141), Ergul (PMID 22404693), Mazzone (PMID 23326337)	
299 - 306	3	**Comment:** There has been substantial new information generated over the last few years validating the six minute walk test (6MWT) as a robust and reproducible measure in DMD and a number of published natural history studies indicate the decrease of distance walked with disease progression. The minimally important clinical difference has been determined, a percent predicted value has been generated and the relationship between decline in the 6MWT and subsequent disease milestones has been reported. Moreover this measure appears to be more sensitive to change than other functional measures in terms of MCID. More recently a statistically different outcome in 6MWT has been reported in a clinical trial of drisapersen versus placebo. **Proposed change:** The guideline should be revised to include the new information available.	**Not accepted**. As stated above since the GL is prepared to provide guidance on general principles in the development of any medicinal products for the treatment in DMD (symptomatic, disease modifying) a balance between not being too specific and providing some general principle requirements is sought.
299-304	6	**Comment:** The guideline should state that 'the 6-minute walk test (6MWT) has been validated in Duchenne muscular dystrophy as a global / integrated measure of multiple systems involved in walking and as a measure of disease progression." Specifically, in DMD the 6MWD correlates with measures of gait pathomechanics / disease progression (stride length and cadence which change with disease progression:	**Not accepted**. It is agreed that the 6MWT can measure ambulation which included the status of several systems. The test has been validated for several conditions and used in clinical trials for DMD among others. Whether it is sensitive to pick up efficacy of products in development will be evaluated based on the data from clinical studies.

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		McDonald 2010a, 2010b), skeletal muscle strength (quantitative knee extension strength per Kg: McDonald 2013a), biomechanical efficiency (heart rate determined energy expenditure index: McDonald 2013a), endurance (10 min continuous step activity with the StepWatch™ accelerometer: McDonald 2009); and gross motor skills (Northstar: Mazzone 2010, Goemans 2013). **Proposed change:** Add the above concepts to the statement that the 6MWT measures "endurance and the ability of walk" (lines 302-303).	
299-306	14	**Comment:** Loss of ambulation is one of the most serious consequences of DMD. The six-minute walk test (6MWT) is an established outcome measure reflecting the global status of all the systems involved in walking, including the neuromuscular, pulmonary, and cardiovascular systems [Takeuchi 2008]. The 6MWT is a clinically relevant, validated, and accepted measure in DMD [Mazzone 2010, McDonald 2010, Prosensa 2011], and has been utilized in clinical trials in various neuromuscular disorders [Rubin 2002, Wraith 2004, Muenzer 2006]. The 6MWT is sensitive to disease progression in the pediatric ambulant DMD population, particularly when evaluated over durations commonly utilized in clinical studies, ie, 6-12 months [McDonald 2013a]. The clinical trials that PTC Therapeutics, Inc. have conducted produced new knowledge about the natural history of DMD for the	**Partly accepted**. It is agreed that loss of ambulation is a critical milestone in the disease progression. It is also agreed that the 6MWT can measure ambulation which includes the status of several systems. The test has been validated for several conditions and used in clinical trials for DMD among others. Whether it is sensitive to pick up efficacy of products in development will be evaluated based on the data from clinical studies. As mentioned it is also very dependent on the stage of disease in which patients are. No changes required.

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		6MWT; while patients 5 - 7 years old can increase six-minute walk distance (6MWD), they then stabilize in walking, slowly getting worse, until their baseline 6MWD is below 350 meters. Once below 350 meters, patients exhibit rapid decline in ambulatory capacity. Hence, the 6MWD result produced from the 6MWT is a clinically relevant measure of disease progression. The degree of change in 6MWD from baseline to one year has been shown to be predictive of the time to loss of ambulation (McDonald 2013a), further demonstrating the clinical importance of the 6MWT in DMD.	
302-306	2	**Comment:** The 6MWT is now extensively used in DMD trials. The caveats about this are difficult to understand and unhelpful. They confuse rather than clarify.	**Partly accepted**. See comment below.
302-306	11	**Comment:** The 6MWT is now extensively used in DMD trials. The caveats about this are difficult to understand and unhelpful. They confuse rather than clarify.	**Partly accepted**. See comment below.
304-306	8	**Comment:** "There are however several caveats with using the 6MWT as an outcome measure, which mainly pertain to learning effect, to inter- and intra-personal variability, and to the definition of a clinically relevant difference" A large set of data have now been published on 6MWT. Epidemiology studies have shown the natural history of 6MWT and have identified the expected changes over time in children with different ages (). Such studies indicate that the learning effect is limited in studies of	**Partly accepted**. The article "The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. McDonald CM., Muscle Nerve. 2010a Apr;41(4): 500-10" outlines the difficulties in applying the 6MWT to DMD boys in general and the need of the development of an adapted version that can be used in DMD clinical trials. Also Wu G. et al., the 6-minute walk test: How important is the learning effect, American Heart Jounal, July 2003, Vol 146, Number 1: 129-133 and Chandra D. et al, Learning from the learning effect in the six-minute-Walk test, American Journal of Respiratory and critical care Medicine , Vol 185, 2012, 686 discusses the drawbacks of the 6MWT, e.g. the learning effect.

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		sufficient duration. Moreover, studies have identified the changes in 6 minute walk distance which are associated with a higher risk of losing ambulation (C. McDonald et al, 2013; Mazzone ES et al, 2013; Henricson E et al, 2012). The intra- and inter-personal variability should be considered with particular attention, and indeed all the on-going clinical trials have implemented very strict quality controls on such a measurement (Bushby K and Connor E, 2011; Mazzone ES et al, 2013; C. McDonald et al, 2013) **Proposed change:** Inter- and intra-personal variability could impact the assessment of 6MWT. Therefore, particular attention should be paid in clinical trials to standardize such a measurement.	Thus we consider it worth mentioning this in the guideline. Based on this and other comments, this section has been revised as follows: *"There are however some issues identified with using the 6MWT as an outcome measure, including a learning effect, inter- and intra-personal variability, the impact of age at baseline and the interference of a growth effect, as well as the lack of long-term data for assessment in case of loss of ambulation…"*
305-307	1	**Comment:** Recent studies have shown that there is no relevant learning effect associated with the 6MWT and have shown minimal clinically important differences (McDonald et al., Muscle & Nerve, pp343-356, 2013; McDonald et al., Muscle & Nerve, pp357-368, 2013). **Proposed change:** We recommend the data and conclusions from the above references are included in the guideline to support the use of 6MWT as an outcome measure in ambulatory DMD trials.	**Not accepted**. Please refer to the comment above. However, the 6MWT is mentioned as an outcome measure in ambulatory DMD studies.
305-307	6	**Comment:** With regard to the *learning effect* in the 6MWT the 6MWD has been shown to be an excellent measure of disease progression in ambulatory DMD	**Not accepted**. Please refer to the comment above.

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		over 12 months (McDonald 2013b, Goemans 2013) and there is absolutely no learning effect when evaluating the decremental changes that occur in patients over 12 months who are over the age of 7 and/or have a baseline 6MWD in the more impaired range (less than 350 meters). Stride length and cadence (steps per minute) are both measures of more severe disease in DMD and these two parameters taken together explain 98% of the variance in 6MWD. **Proposed change:** Delete any reference to *learning effect* with the 6-minute walk test as there is no data to support this concept.	
305-307	6	**Comment:** The statement 'There are however several caveats with using the 6MWT as an outcome measure, which mainly pertain to a learning effect, to *inter- and intra-personal variability…'* is mis-leading and not supported by recently published data. In fact, intra-personal variability is actually better with the 6MWT as compared to strength, and timed function tests. All clinical endpoints used in ambulatory DMD (6MWD, quantitative lower extremity strength, timed function, Northstar, etc.) show increased variability over the course of 12 months in DMD. This increasing variability is due to variability in disease progression in DMD among patients followed longitudinally and is NOT specific to any single endpoint including the 6MWT (McDonald 2013b). The ratio of MCID (based on statistical distribution properties) to mean baseline	**Not accepted**. Please refer to the comment above.

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		value is lower for the 6MWD in comparison to strength and timed function values. This likely accounts for the increased sensitivity / responsiveness of the 6MWD to treatment effects observed with virtually every ambulatory trial conducted recently in DMD. Proposed change: Delete the statement that a caveat with the 6MWT pertains to inter- and intra-personal variability.	
305-307	6	**Comment:** The guideline states that "There are however several caveats with using the 6MWT as an outcome measure, which mainly pertain to the definition of a clinically relevant differences." The Minimal clinically important difference (MCID) for the 6MWD based on statistical distribution properties was approximately 30 meters (McDonald 2013a). Recent data confirms that a 30 meter decrement in 6MWD from mean baseline predicts the likelihood of experiencing 10% deterioration in ambulatory function over the next 12 months (McDonald 2013b). Deterioration in ambulatory function by 10% or greater over 12 months is predictive in DMD of loss of ambulation over the next 4 years (McDonald 2012, McDonald 2013a, 2013b). In addition, a 30 meter change in 6MWD has been shown to be associated with loss of ambulation of 2 years (Mazzone 2013). The correlation between baseline 6MWD and *weeks to loss of ambulation* was r=0.85 in one recent trial (McDonald 2013b). Finally, Henricson and colleagues	**Not accepted**. Please refer to the comment above. 30 meters are not specifically mentioned in this guideline as being the MCID in 6MWD for DMD patients. The discussion about the minimal clinically relevant difference is still ongoing and before a consensus among stakeholders is reached, it is not considered appropriate to include in the guideline a specific figure as suggested. The GL is meant to provide more general guidance on companies developing products for the treatment of DMD.

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		(2013) recently showed there is a strong correlation between 6MWD and the global Pediatric Outcomes Data Collection Instruction (PODCI) patient-reported outcome measure (adjusted R squared = 0.83) which focuses on global QOL (transfers and basic mobility, sports and physical functioning, pain and comfort, and upper limb function). A 30-meter change in 6MWD change is associated with a clinically meaningful change in the PODCI, a patient/parent reported outcome measure of functional ability (Henricson 2013). This supports the notion that preservation of a mean of 30 meters over a 48 week period is meaningful in terms of activities of daily living for boys with DMD. **Proposed change:** Delete the statement that "there are however several caveats with using the 6MWT as an outcome measure, which mainly pertain to … the definition of a clinically relevant differences." Update the discussion with the new referenced data that supports the 6MWD as a clinically meaningful endpoint. It is strongly suggested that 30 meters should be specifically mentioned in this guideline as being the MCID in 6MWD for DMD patients. Published literature strongly suggests that a 30 meters change over 12 months is clinically meaningful to patients and their families.	
307-313	3	**Comment:** While we agree that there are concerns with potential errors and variability in timed-function	**Partly accepted.** Sentence has been rephrased as follows: *"Timed-function tests to assess timed activities exist for*

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		test measurements, we don't agree that they are no longer useful or with the suggestion that they are no longer currently being used and still provide useful information. They continue to be used and provide relevant and important linear data. By using calibrated timing devices, and through incorporating some of these test into the NSAA, there is confidence in the reported measurements. Improved training, through video review and close collaboration with international groups, assessments are felt to be much more accurate than suggested by this section of the guidance. **Proposed change:** Modify the paragraph to reflect that timed function test continue to be used clinically and with better quality control and calibrated timing devices, there is much better confidence that these test are providing meaningful and accurate measurements.	*climbing a short flight of steps, walking a short, predefined distance (usually 10 meters), rising from the floor, and sit-to-standing from a chair. Timed- function tests continue to be used clinically and in study programmes because they provide relevant information. There can be problems with assessors' error in timing (especially for very brief tests as sit-to-stand from a chair), as the observed value of any measures is equal to the true value plus the degree of random error or bias [16]. Due to typically huge baseline variability and small changes from baseline, the clinical relevance of results is often difficult to evaluate. However, by incorporating such activities into standardised functional rating scales (e.g. NSAA includes timed rise from floor and timed 10 meter run) and by using appropriate calibrated timing devices, it may be possible to increase confidence in the accuracy of these tests, if well substantiated."*
308-314	1	**Comment:** We propose to change the text of this paragraph – see below. **Proposed change:** "Timed function tests continue to be used clinically and in trials because they provide relevant and meaningful linear data. By incorporating such activities into standardised functional rating scales (e.g. NSAA includes timed rise from floor and timed 10m run) and using appropriate calibrated timing devices confidence in the accuracy of these	**Partly accepted**. See comment above.

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		tests is high. Improved collaboration between international groups and standardised training procedures, including quality control by video review of assessments ensures accuracy."	
315	1	**Comment:** We propose to expand the text of this sentence – see below. **Propose change:** "Measures for non-ambulant patients have been recently developed with the aim of providing data on clinically meaningful change. For example the performance of upper limb scale (PUL) and associated PROM (Mayhew, Eagle, Mazzone 2013). The recent development of these scales has been a collaboration between patients their advocacy groups and a multi-disciplinary international team of experts. This has ensured a clear link between measured performance and meaningful activities. Functional ability over the long term is measured with the validated Egen Klassifikation scale (EK)." Reference: Development of the Performance of the Upper Limb (PUL) module for Duchenne muscular dystrophy. Anna Mayhew, Elena Mazzone, Michelle Eagle, Tina Duong, Maria Ash, Valerie Decostre, Marlene Vandenhauwe, Julaine Florence, Marion Main, Flaviana Bianco, Erik Henrikson, Laurent Servais, Giles Campion, Elizabeth Vroom, Valeria Ricotti, Natalie Goemans, Craig McDonald, Eugenio Mercuri, on behalf of the PUL	**Partly accepted**. The sentence in line 314 (?) will be rephrased as follows: *"Recently, also specific measures for non-ambulant DMD patients have been developed with the aim to provide data on clinically meaningful changes, for example the Performance of Upper Limb scale (PUL). Functional ability over the long-term can be measured with the validated composite Egen Klassifikation (EK) scale."*

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		working group. DMCN, 2013	
315	4	**Comment:** This comment should reflect current status. Specific functional tests for non-ambulant patients are being developed, for example the Performance of Upper Limb (PU) and PROM scales (Mayhew et al., on behalf of the PUL working group. DMCN – in press 2013) and will improve evaluation of performance and correlate to validated measures, such as the Egen Klassifikation scale.	**Partly accepted.** See comment above.
315-320	3	**Comment:** The guidance document should reflect the significant amount of work and new data that has become available regarding the various tools that are being used. For example, the performance of upper limb scale (PUL) and the RPOM have ensured a link between measured performance and meaningful activities. Another example noted earlier, the NSAA combines clinically relevant functional performance with two timed tests. Recent publication of a linearized scale for ambulant DMD boys has addressed the issue of summed scores. Longer term data are being collected for NSAA, 6 MWT and times tests and will be available in the near future. **Proposed change:** Modify the text so that the significant amount of work and the new data that has become available regarding the various tools that are being used are properly reflected.	**Partly accepted.** See comment above.

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315-320	14	**Comment:** The minimal clinically important difference (MCID) for 6MWD for DMD patients has been determined by two distribution-based methods to be 28.5 to 31.7 meters (McDonald 2013b). A 30-meter change in 6MWD change is associated with a clinically meaningful change in a patient/parent reported outcome measure of functional ability (the Pediatric Outcomes Data Collection Instruction – PODCI; Henricson 2013), supporting the notion that preservation of a mean of 30 meters over a 48 week period is meaningful in terms of activities of daily living for boys with DMD. A 30-meter change has direct relevance to DMD patients' daily lives, eg, ability to climb stairs, reduction in accidental falls, and time spent in wheelchair. In addition, this value is also consistent with multiple published studies spanning a variety of diseases as a clinically relevant benchmark of treatment effect for the 6MWT (Ruben 2002, Wraith 2004, Muenzer 2006, van der Ploeg 2010, McDonald 2013b). Evidence of the meaningfulness of 30 meters in the 6MWT is also seen in a recent analysis of longitudinal 6MWT test data by an independent group of experts of a European cohort of patients (Dr. Eugenio Mercuri, Unpublished Data). The results show that for every 30-meter incremental decrease in baseline 6MWD the percentage of patients who become non-ambulatory over the following 2 years increases substantially.	**Not accepted**. The 30 m change in 6MWD has been discussed in two contexts; 30 m preservation over 48 weeks (as compared to placebo) or in absolute terms. The discussion about the minimal clinically relevant difference is still ongoing and before a consensus among stakeholders is reached, it is not considered appropriate to include in the guideline a specific figure as suggested, neither in meters change on 6MWT nor in time period. The GL is meant to provide more general guidance on companies developing products for the treatment of DMD.

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		PTC Therapeutics, Inc. clinical trial results, external published literature, and the most recent unpublished results are unified in their assessment of a 30-meter change in 6MWD as the MCID for the 6MWT in DMD. Thus, it is strongly suggested that 30 meters should be specifically mentioned in this guideline as being the MCID in 6MWD for DMD patients.	
316-321	1	**Comment:** These issues are being addressed particularly in assessment of ambulant patients. The NSAA combines clinically relevant functional performance with two timed tests. **Proposed change:** "Recent publication of a linearised scale generated by modern psychometric analysis (Rasch) for use in ambulant DMD has addressed issued raised by sum scores and has provided a definition of MID (Mayhew 2013 – in press). The techniques employed for this functional rating scale are currently being employed in other functional rating scales, e.g. Performance of the Upper Limb (Mayhew et al., 2013). Long term data are being systematically collected internationally for NSAA, 6MWT, timed tests."	**Not accepted.** As stated above since the GL is prepared to provide guidance on general principles in the development of any medicinal products for the treatment in DMD (symptomatic, disease modifying) a balance between not being too specific and providing some general principle requirements is sought.
318 to 320	5	**Comment:** Clarification is needed on the statement 'to combine different assessment tools' and whether this is referring to a composite endpoint? We presume not since the example given (functional scale and a timed-function test) would mean a composite of a potentially well-validated scale with accepted clinical relevance	**Agreed**. These lines do not imply the use of a composite endpoint, but the use of several endpoints measuring different domains with the purpose to measure different aspects and translate them into clinical relevance. **Outcome:** the text has been revised as follows:

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		e.g. MFM with time-function test that is stated in the guidance to have 'huge variability and small changes' with questionable relevance to be used as a secondary only. If not a composite endpoint we presume this is referring to having both endpoints in the trial but this should be clarified in the final guidance.	*"Taking into account the heterogeneity in DMD and BMD, disease-specific scales and tools that cover a broader range of disease severity should be applied in parallel. It is also recommended to use different assessment tools, e.g. a functional scale and a timed-function test, to sufficiently assess relevant changes in motor function (e.g. endurance) and to transfer results into clinical relevance."*
321-332	7	**Comment:** Upper limbs assessment in non ambulant patients is crucial and remains a challenge so we propose to add information on new tools developed to assess upper limb strength and function. We have written a new paragraph and we propose to include the following reference in the bibliography list : *"Innovative methods to assess upper limb strength and function in non ambulant Duchenne patients. L Servais and al. Neuromuscul Disord 2013 Feb;23(2):139-48"* A prospective longitudinal study is ongoing to evaluate the sensitivity of these different methods (a new publication is under preparation). **Proposed change:** Assessment of muscle strength: Muscle strength should be evaluated by clinical assessment using a validated tool. Options include manual muscle testing (MMT) also used as composite scores and quantitative muscle testing (QMT) scores such as hand-held-dynamometry (HHD). Both tools have their shortcomings. HHD is often	**Accepted.** The development of new assessment tools for upper limb function and strength are very welcomed. In this respect the suggestion to include a paragraph with reference to recently developed tools is agreed and has been included with modified wording.

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		classified as preferred measure as it provides quantitative parametric data, whereas MMT is a subjective measurement method that depends on the perception of the assessor. The clinical significance of HHD data may, however, be less obvious that of MMT as the correlation of a value in Newtons or kilograms with a change in muscle grade, or a change in functional ability is not clear. In contrast, with MMT, a grade less than 3 means that the participant cannot gain full range of movement against gravity, thus giving useful clinically relevant information for the evaluator [13]. New tools have been developed to assess upper limb strength and function in non ambulant patients(pinch, grip and wrist flexion and extension)(add reference to the bibliography list)	
322-331	5	**Comment:** We are concerned with the use of Manual muscle testing (MMT) as a reliable surrogate end-point, particularly in small clinical trials. MMT is categorical, crude and has very poor test-retest reliability all resulting in potentially poor assessment of muscle strength improvement. As noted in the guidance, Quantitative muscle testing (QMT) is a continuous measure. It may be assessed fixed vs portable-fixed vs portable. It is proposedthat more should be done within the guidance to outline the risks of the approach with the use of MMT and more focus be placed on the role of QMT or assessment of physical performance testing, which can be correlated to clinically significant improvements, such as 6MW, which also has regulatory precedence. Both QMT and measures of physical function can be assessed in both ambulatory and non-ambulatory subjects and therefore could allow for incorporation of broad range of study subjects.	**Partly accepted**. The section has been revised as follows: "*Muscle strength should be evaluated using a validated tool. Options include quantitative muscle testing (QMT) scores such as hand-held-dynamometry (HHD) and manual muscle testing (MMT).* *Both tools have their shortcomings. HHD is often a preferred measure as it provides quantitative parametric data, whereas MMT is a subjective measurement method that depends on the perception of the assessor. The clinical significance of HHD data may, however, be less obvious than that of MMT as the correlation of a value in Newtons or kilograms with a change in grade of muscle strength, or a change in functional ability is not clear[16].* *New tools have been developed to assess upper limb strength in non-ambulant patients (e.g. pinch (MyoPinch), grip (MyoGrip) and wrist flexion and extension (MyoWrist) strength) [28], which may be considered if adequately validated."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: Muscle strength should be evaluated by clinical assessment using a validated tool. Options include ~~manual muscle testing (MMT) also used as composite scores and~~ quantitative muscle testing (QMT) scores such as hand-held-dynamometry (HHD) and manual muscle testing (MMT) also used as composite scores. Both tools have their shortcomings, particularly MMT. HHD is often classified as preferred measure as it provides quantitative parametric data, whereas MMT is a subjective measurement method that depends on the perception of the assessor. MMT is a simple categorical tool that, has poor test-retest reliability, and may not be suitable for use in small clinical trials. The clinical significance of HHD data may, however, be less obvious than that of MMT as the correlation of a value in Newtons or kilograms with a change in muscle grade, or a change in functional ability is not clear. ~~In contrast, with MMT, a grade less than 3 means that the participant cannot gain full range of movement against gravity, thus giving useful clinically relevant information for the evaluator.~~	
334-339	1	**Comment:** There is limited experience of these in the DMD population, while on the contrary there is recent and convincing data on the PODCI and its correlation with functional activities (Henricson et al., 2013).	**Not accepted**. See comment below.
334-338	3	**Comment:** The guidance makes reference to the past. It should also reflect more current information regarding ADLs. For example there is recent data on the PODCI demonstrating correlation with functional activities (Craig McDonald et. al.)	**Not accepted**. Although these data are appreciated, they are based only on one recent publication, which still needs a wider confirmation.

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		Proposed Change: The text should be revised to reflect the above.	
340-345	1	**Comment:** This should not be limited to tracheostomy only. What about the requirement for ventilation for at least part of the day, in addition to night ventilation? Other criteria could include coughing or incidence of pneumonias.	**Comment appreciated**. However, to mention further criteria would go beyond the scope of this guideline. It is recommended to discuss these endpoints case by case via scientific advice.
346-352	4	**Comment:** This statement should reflect current status. Sleep disorders resulting from compromise of respiratory function constitute an adverse effect of disease progression on the well being of patients affected with DMD. In addition, clinical tools such as the Sleep Disturbance Scale for Children are suitable for assessing/quantifying such compromise. Based on these observations, we propose that favourable effect of treatment on the sleep disturbance that results from respiratory compromise would be a clinically meaningful efficacy variable in the non-ambulatory population that should be reflected in the guideline.	**Comment appreciated**. However, to mention further criteria would go beyond the scope of this guideline. It is recommended to discuss these endpoints case by case via scientific advice.
353-356	1	**Comment:** Cardiac MRI should be included in this section.	**Accepted.**
353	12	**Comment:** MRI should be see as key means for measurement as in many reports it has been the only means to spot early sub clinical cardiac involvement such as fibrosis. Multiple studies involving MRI are underway in the Duchenne Community (ImagingDMD	**Accepted.**

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		being one). **Proposed change:** Included MRI as key example of cardiac monitoring	
357-360	1	**Comment:** Further research is needed to see if the PedsQL is sensitive to detect changes in DMD patients during a clinical trial. Data will soon be available on the use of the Kidscreen.	**Comment acknowledged.**
357-359	6	**Comment:** The guideline states that "a disease specific module of the PedsQL (Pediatric quality of life inventory), the PedsQL 3.0 Neuromuscular Module (NMM) has recently become available that could be administered together with the PedsQL 4.0 Generic Core Scales PedsQL. Recent published data documents the Pediatric Outcomes Data Collection Instruction (PODCI) as being more responsive and more closely associated with clinical measures of disease progression in DMD in comparison with the PedsQL (McDonald 2010c, Henricson 2013). The generic PedsQL is not particularly responsive to disease progression in DMD. There is no data to suggest the PedsQL 3.0 NMM is a useful PRO for DMD clinical trials. Unpublished data from Mercuri and colleagues show little change in the PedsQL NMM over the course of 12 months in a DMD natural history cohort. The current Lilly sponsored Tadalafil trial is the largest phase 3 registration trial ever conducted in DMD and this trial as well as a phase 3 registration	**Partly accepted** as the proposed changes would go beyond the scope of this guideline. However, the PODCI has been included.

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		trial of ataluren (PTC Therapeutics) are both utilizing the PODCI based on these published data. **Proposed change:** State that two studies indicate the PODCI as being more closely associated with measures of disease progression in ambulatory DMD in comparison with the PedsQL generic scale. State that no longitudinal data has been published to date with the NMM. State that the PODCI global scale, PODCI transfers and basic mobility scale, and the PODCI sports and physical functioning scales are strongly correlated with both the 10 meter run/walk velocity and 6MWD in DMD (Henricson 2013).	
361-363	1	**Comment:** Cognitive deficits in DMD are not progressive. This would only be relevant for those drugs that cross the blood brain barrier. Also, behavioural changes could also be influenced by positive effects or changes that make them feel better or have more energy. **Proposed change:** delete 'or lack of deterioration in' from lines 362-363. This should now read: improvement of cognitive function might be a relevant clinical achievement.	**Accepted with slightly modified wording.**
367-376	3	**Comment:** While we agree that currently dystrophin expression has it limits as a surrogate, the guidance should reflect the progress that has been made in this area. As presented at the TREAT NMD workshop g in	**Partly accepted.** With regard to dystrophin it is explicitly mentioned that it is an accepted biomarker for proof of PD effect (in products with mechanism of action inducing dystrophin production), but is not recommended as surrogate

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		London recently, recent advances in the field have resulted in a robust, reproducible assay. Through an international collaborative effort to standardize dystrophin quantification between industry and academia (Biological Outcome Measures (BOM)group) it was shown that it was possible to standardize distrophin measurments across different laboratories. More work needs to be done, but dystrophin remains a promising biomarker and work will continue for its further development. **Proposed Change:** The guideline should be revised to reflect the above.	marker to measure efficacy, since quantification and therefore measurement of change is problematic. In addition the finally important outcome for the patients is any clinical meaningful change. Therefore dystrophin is not accepted as a primary efficacy endpoint in phase 3 studies.
367-371	12	**Comment:** Current mechanisms for measuring this are available: Quantification of dystrophin immunofluorescence in dystrophinopathy muscle specimens. (Flanigan etal. 2012) With low levels of expression showing benefit (The Effects of Low Levels of Dystrophin on Mouse Muscle Function and Pathology) along with the current stabilization at 84 weeks of boys on the phase II Eteplirsen trial, that showed clinical benefit only after dystrophin production (post week 24), together with the natural shortened dystrophin production in Becker Muscular dystrophy, where ambulation and life expectancy are considerably better than that of Duchenne, must surely show a correlation between dystrophin production and clinical benefit, for use as a	**Not accepted** as the definition of prerequisites to establish dytrophin as surrogate for clinical efficacy would go beyond the scope of this guideline.

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		biomarker for primary endpoints. The ability to use dystrophin as a surrogate marker for efficacy is crucial in further exon skipping trials where a platform approach can be used to get multiple drug targets into trial in parallel. If pharmacodynamic tests are required for each new antisense (given the same backbone), then these trials for the multiple mutations will take years. This is time that Duchenne boys do not have. All parties agree that exon skipping (currently the best hope for therapy for all boys at present) is better at early stages of the disease where more muscle can be protected. Potentially leading to own boys ability to build muscle previously damaged. Later stages where fibrosis and necrosis have taken over, leave little space for muscle fibers to grow to be protected. **Proposed change:** Establish what is needed to facilitate correlation of dystrophin as a surrogate to clinical benefit, so a specific goal is set to be reached, and industry and researchers can have confidence in obtaining evidence for their surrogate. At present the existance of an unknown quantity means this issue has remained unresolved since the 2009 meeting the duchenne community had with the EMA in London.	
367-377	5	**Comment:** It is considered that methodologies to quantify the amount of dystophin protein from muscle biopsies have improved in recent years with the introduction of image analysis software. Therefore, the	**Not accepted**. See comment above.

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		quantification dystrophin protein from muscle biopsies can now be considered a secondary objective rather than an exploratory objective in trials. In addition we consider that the detection of altered mRNA expression could be used as a pharmacodynamics marker for proof of concept for restoration of dystrophin protein expression as increases in mRNA levels are often an indicator for increase protein expression. **Proposed change:** 'Serum CK levels, muscle dystrophin expression and reduction in inflammatory infiltrates still have their limitations as surrogates. ~~Based on the fact that the currently existing methodologies to quantify dystrophin from muscle biopsies are debatable regarding the robustness and the precise quantification of extremely low levels of dystrophin, quantification of dystrophin protein from repeat muscle biopsies currently could be considered only as an exploratory endpoint for clinical efficacy.~~ Methodologies to quantify dystrophin from muscle biopsies are emerging and the robustness and precise quantification of extremely low levels of dystrophin is improving due to the introduction of image analysis software. The quantification of dystrophin protein from muscle biopsies currently could be considered as a secondary endpoint for clinical efficacy. In cases where the mechanism of action of the therapy is related to the restoration of dystrophin expression, detection of altered mRNA or dystrophin protein in muscle tissue could provide supportive information as a pharmacodynamic marker for proof of concept.' 'At this stage, there is no suitable biomarker that could be a primary ~~or key secondary~~ endpoint in phase III studies, but their development is encouraged.'	

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376-377	4	**Comment:** We note that imaging technologies such as MRI can follow disease activity sensitively, and have been correlated with functional status. This is true for MRI of skeletal and cardiac tissue. While such measures may not be adequate surrogate markers that can provide primary evidence to support approval at this point, it should be noted that they could be utilized in dose-response analyses as well as to extrapolate efficacy findings to other populations. This could provide for the ability to examine slowing of disease progression in younger children, and perhaps the non-ambulatory, for which an adequate primary endpoint may be insensitive or currently not validated or available.	**Not accepted** as there is currently a lack of data to support evidence of imaging technologies to serve as endpoint in dose-response studies or for extrapolation.
380-405	2	**Comment:** The general comment 6 above is repeated here. A great deal of extrapolation is possible and ethically necessary in a responsible way to allow the developments of AONs for all the mutations as expeditiously as possible.	Please refer to the answer to the general comment point 6.
380-405	11	**Comment:** The general comment 6 above is repeated here. A great deal of extrapolation is possible and ethically necessary in a responsible way to allow the developments of AONs for all the mutations as expeditiously as possible.	See comment above.
381-385	4	**Comment:** An additional type of extrapolation, in addition to those mentioned, is extrapolation between age groups. As explained below, this is an important concept given the lack of clinically relevant endpoints especially in the youngest patients. Suggestions for amended text are provided (new text is shown ***bold italic***):	**Partly accepted.** Extrapolation between age groups, from older to younger patients, e.g. due to the lack of available clinical endpoints especially in the youngest children, has been included under the first question of extrapolation.

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		"The question of extrapolation in fact concerns ***three*** different aspects: The first is the extrapolation of efficacy to various degrees of disease severity in a population with the same (group) gene defect (e.g. that can be corrected by the same exon skipping strategy). The second is the extrapolation of efficacy results between patient populations with different groups of mutations. The third is extrapolation, based on pharmacodynamic markers, between populations with available clinical endpoints and those without available clinical endpoints."	
381-406	4	**Comment:** This section would benefit from some additional discussion about the appropriate methods to support extrapolation from populations that have available practical clinical endpoints to those that do not. For example, in young children there is a period with limited but real functional deficits. Given the lack of available endpoints and the lack of profound functional deficits, conducting a study in this population may not be practical, while the use of disease modifying agents in this population may be critical to long-term disease management. Given this, as we have noted in comments above, some discussion of the use of biomarkers or imaging technologies to support extrapolation to these populations would be useful.	**Partly accepted** as extrapolation between age groups, from older to younger patients, e.g. due to the lack of available clinical endpoints especially in the youngest children, has been included under the first question of extrapolation. However, as this is a case by case decision, for further discussion on extrapolation CHMP scientific advice is recommended.
381	4	**Comment:** This section should provide guidance regarding extrapolation of efficacy for compounds that	**Not accepted.** The possibility for extrapolation is discussed in the GL and has been amended. Please note that the GL is

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		do not target a specific mutation and that would be expected to provide benefit to all DMD patients given the common underlying pathophysiology (dystrophin deficiency) of the disorder.	aimed for all possible medicinal products for the treatment of DMD. As this is a case by case decision, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.
382-405	3	**Comment:** While acknowledging the challenge of the topic, developing guidance around extrapolation is essential for AONs that target the rarer target exons, where it will not be possible to demonstrate efficacy in all subsets, and subgroups of patients due to the lack of availability of subjects. Demonstrating efficacy and safety for all subsets of patients with various degrees of disease severity in a population with the same (group) gene defect, should inform the potential of benefit with more rare target exons assuming one could demonstrate efficacy in at least the ambulant population where possible, and demonstrate a positive biomarker (e.g. dystrophin) effect. For the extremely rare exon targets, demonstration of dystrophin effect, or some other biomarker, may be the only viable option of demonstrating an effect that has been previously linked to clinical efficacy in other programs. Further follow-up to monitor the efficacy and safety of these compounds that have relied on extrapolation could be accomplished through post-market programs, e.g. registries, etc. This approach could be also be viable where extrapolation was utilized for subsets of patients (within the same gene defect) where due to limited numbers of patients, it was not feasible to generate	**Partly accepted.** The possibility for extrapolation from older to younger is now discussed in the GL and has been amended. Please note that the GL is aimed for all possible medicinal products for the treatment of DMD. As this is a case by case decision, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.

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		sufficient efficacy information (e.g. older boys, non-ambulant boys, etc.). Demonstrating the pharmacodynamic response is similar in various stages of the disease would provide further justification for this approach. **Proposed Change:** Further guidance on the use of extrapolation for subgroups of the same mutation or for rare mutations needs to be incorporated.	
389-391	1	**Comment:** states that exon skipping will likely restore dystrophin irrespective of disease state: we disagree. Exon skipping targets dystrophin transcripts which are produced by muscle tissue. Thus exon skipping is anticipated to have more impact in younger children than older children with DMD. **Proposed change:** Therapies that make use of dystrophin transcripts rely on muscle quality as only muscle produces dystrophin transcripts.	**Accepted**. The paragraph has been rephrased as follows: *"As therapies (e.g. exon skipping) that make use of dystrophin transcripts rely on muscle quality, these therapeutics might be expected to have more impact on muscle strength and function in younger children than in older children with DMD (i.e. due to earlier than more advanced stages of muscle dystrophy)."*
396-397	12	**Comment:** As mentioned above, if exon skipping therapies or other therapies that return the reading frame for shorted dystrophin production, then one would essentially be creating a Becker like phenotype. Cocktail therapies to prevent fibrosis or increase muscle production/decrease muscle inhibition would then be suitable for natural Becker and treatment induced Becker groups. Should these really be segregated?	Please refer to the comment above. However, in any case, a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.

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399-406	1	**Comment:** This paragraph is very conservative. There is good evidence from the DMD/IMD and BMD population that any dystrophin is better than none and that it is associated with a functional benefit (with the exceptional exceptions of in-frame deletions completely lacking the actin binding domain or the beta DG binding domain). Therefore, we would hope that whenever appropriate we would use dystrophin as a pharmacodynamics marker of response, but that large studies will not be necessary to demonstrate efficacy when testing novel compounds such as novel antisense compounds, for which there will not be a large population to test.	**Comment acknowledged.** The flexibility and discussions about a possible limited package for assessment have been ongoing. Please note that the GL is aimed for all possible medicinal products for the treatment of DMD. As this is a case by case decision, for any detailed consideration a CHMP scientific advice should be sought to discuss the most appropriate strategy for development.
404-405	12	**Comment:** Agreed – Allowing trials with similar mechanism of action (i.e. exon skipping) that uses a common surrogate (dystrophin production) against the background of natural history data, would facilitate much faster development of further exon skipping compounds for even the rarer exon skipping compound requirements. **Proposed change:** Be more specific about whether different exon skipping mutations could be allowed in the same trial if a common surrogate marker (i.e. dystrophin) could be validated and correlated to clinical benefit.	**Not accepted.** See comment above.
407-411	1	**Comment:** states that the mdx model is a poor model	**Accepted.** The paragraph has been rephrased as proposed:

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		for DMD phenotype and the predictive value of GRMD is not known. We agree, but would like to add that both models have been pivotal to gain insight into the pathology and that the mdx model has been very useful to develop many therapeutic approaches, in spite of its limitations. In particular it is well suitable for genetic approaches that are mainly discussed in the document. The reason the GRMD is of limited predictive value is that the phenotype varies a lot and usually only a few dogs are included in tests. TREAT-NMD has produced a number of standard operating procedures for enhancing predictability of drug testing in the mdx mouse model and these are increasingly used worldwide (Nagaraju et al., 2009; van Putten et al., 2010; van Putten et al., 2012). We would like to add that properly conducted mouse studies, along with a closer collaboration between pre-clinical and clinical scientists, help to prioritize best candidates or best approaches for clinical trials and likely reduce the risk of failure during translation. Many papers are now available to outline how to properly use the mdx mouse (Grounds et al., 2008; Willmann et al., 2012) and evidence are being produced in favour of a better matching of data set in mice and patients (Heemskerk et al., 2009; Heemskerk et al., 2010; Tanganyika-de Winter et al., 2012) **Proposed change:** We suggest modifying lines 408-410 as follows: The proposed mechanism of action of a new product should be described and discussed in	*"The proposed mechanism of action of a new product should be described and discussed in relation to possible testing in available animal models. The widely used mdx mouse and the golden retriever muscular dystrophy dog are of value for pathology studies and for pre-clinical tests of therapeutics. Adoption of standard operating procedures and of controlled experimental settings is highly recommended to minimise the known limitations of both models and enhance predictability of data."*

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		relation to possible testing in available animal models. The widely used mdx mouse and the golden retriever muscular dystrophy dog are of value for pathology studies and for pre-clinical tests of therapeutics. Adoption of standard operating procedures (such as those developed by TREAT-NMD) and of controlled experimental settings is highly recommended to minimise the known limitations of both models and enhance predictability of data (www.treat-nmd.eu/research/preclinical/dmd-sops/; Nagaraju et al., 2009; Willmann et al., 2009).	
407-411	3	**Comment:** The guidance creates a negative impression regarding the available animal model that doesn't do justice to the role they have played in the field. While not perfect, the mdx model (and less so the GRMD model) have been important in advancing insight into the pathology of DMD. Further the mdx model has been invaluable in developing therapeutic approaches that are currently in clinical testing. The use of standardized operating procedures, particularly with the mdx model, has improved their utility for the predictability of drug testing. **Proposed change:** The guideline should be revised as per the comment above.	**Accepted**. See comment above.
407-411	5	**Comment:** It is suggested that this paragraph (lines 407-411) is rewritten as follows to place more emphasis on data collected from patient donor tissues and from clinical trials in the determination of a	**Partly accepted**. See comment above.

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		proposed mechanism of action. In addition, the mdx mouse model is considered to be mild model of the DMD phenotype and can be useful in reflecting the earlier stages of the disease. **Proposed change:** The proposed mechanism of action of a new product should be described and discussed in relation to possible testing in available ~~animal models which are currently limited. (E. g. the mdx mouse is considered a poor model of the DMD phenotype,~~ patient donor tissue and the changes in biological parameters seen in clinical studies with patients or healthy volunteers (if appropriate). Some efficacy and distribution studies may be performed in animal models of DMD using validated protocols. The *mdx* mouse is a mild model of the DMD phenotype and best reflects the earlier stages of the disease, while the predictive value of results in the golden retriever muscular dystrophy dog is still unknown~~).~~ ~~In addition, the changes in biological parameters seen in patients or healthy volunteers (if appropriate) should be addressed.~~	
408-411	4	**Comment:** This statement should reflect current status. The predictive value of the mdx mouse and GRMD models is not known. However, the development of standard operating procedures when using these models will significantly improve the value of preclinical evaluations. Researchers should be encouraged to utilize these procedures when testing compounds for the possibility of future clinical study.	**Accepted.** See comment above.
438-439	4	**Comment:** It should be noted in this section that various measures, such as isolated muscle function and perhaps even imaging, could be justified for use as endpoints in establishing proof of mechanism and in	**Not accepted**- no data were provided demonstrating their appropriateness as surrogate endpoints.

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		establishing dose-ranging. This is inherently challenging is very small populations.	
441-444	4	**Comment:** It should be noted in this comment that the age at diagnosis for most patients with DMD is age 2-5. Therefore, in the absence of a large identified patient population, clinical investigations of treatments for DMD in patients < 3 years of age are not operationally feasible. Based on these observations, a prospective statement regarding waiver for investigation of interventions in this age group would be of benefit in guiding plans for investigating treatments of DMD across the various paediatric age groups.	**Not agreed with**; the section on extrapolation covers this issue.
441-451	3	**Comment:** The guidance should acknowledge that, depending on the subset of the disease severity, and the rarity of the target exon being studied, it may not always be practical, and may actually be impossible, to "study the efficacy and safety of the product" in a broad range of patients in confirmatory trials. With few patients, and in even more rare mutations, "separate studies" "including sufficient numbers to allow for comparison in the different stage groups" is not always feasible. This section should acknowledge this fact and should refer to the section on extrapolation. Without developing an acceptable strategy for extrapolation, developing viable therapeutic options for rare exons will not achieved. **Proposed change:** Further guidance on the use of extrapolation for subgroups of the same mutation or	**Comment acknowledged**. The possibility for extrapolation is discussed in the GL and has been amended. Please also refer to comments above.

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		for rare mutations needs to be incorporated.	
448 - 451	5	**Comment:** We support the draft guideline position that a single trial could be sufficient for a confirmatory study given the orphan status of DMD. However, it would not be feasible to have a single study which would cover different disease stage groups, as depending on the status of the disease different primary endpoints would be more suitable. For example, a 6MW primary endpoint may be suitable for ambulatory patients, however, it would not be suitable for non-ambulatory patients. While a single study would not cover all disease subsets this should still be sufficient for the registration for DMD at least in the subset of patients studied given the significant unmet medical need. **Proposed change:** "Separate studies are preferred according to the disease stage and/or the outcome parameters, or at least those groups should be studied in a single trial with pre-specified stratification of subgroups including sufficient number of patients to allow for comparison in the different disease stage groups in order to obtain a broad indication. However, consistency over the subgroups would add to supportive evidence. A single study in a particular disease stage may be considered sufficient; however, this would only result in an indication in a specific sub-group."	**Not accepted.** The proposed text is too restrictive. Whether a clinical study in a subset of the entire DMD population may be sufficient for discussion of the benefit/risk for all stages of the disease would depend on several factors, e.g. on the mechanism of action, the treatment goal and results obtained, among others. This is therefore considered a matter of assessment of the entire dossier and B/R discussion for each individual case. As such no specific claims can be made in this guideline.
456-491	7	**Comment:** For some advanced therapy medicinal products (ATMP) due to the route of administration which is very invasive it should be very difficult to organize controlled studies (double-blind , parallel-group)and even more with a placebo arm for mainly ethical reasons.	**Partly accepted.** The difficulties in organizing placebo controlled studies with some ATMPs are recognized both for orphan and non-orphan diseases. Therefore in some specific cases alternative designs may be considered. However it is essential to have some control in the studies. Therefore all possible efforts for controlling data should be encouraged. The

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		As a consequence it is important to authorise confirmatory clinical trials without controlled arm mainly in the case of the orphan drugs. **Proposed change:** 7.6.1. Short-term studies Study design Confirmatory trials to show symptom or disability improvement should be randomised, double-blind, parallel-group and possibly placebo controlled, when it is feasible. The preferred design to show a disease modifying effect or survival increasing is a time to event design where the event is defined as worsening on a functional or symptom scale or time to milestone event.	guideline now considers the use of recent natural history cohorts as an option for small patient populations with a very rare genetic defect in which controlled studies are not feasible and if the use of such controls can provide an adequate comparison. However, specific study designs should be discussed with regulators in the form of a scientific advice.
457-461	2	**Comment:** Due to the small patient population, open label trials with outcome measures approved by the regulator should be encouraged.	**Not accepted**. The difficulties in organizing placebo controlled studies in this disease are recognized. In fact placebo controlled in this case does not mean no treatment at all, but comparison of the tested compound in addition to standard of care (including corticosteroids). Open label single arms studies are not very helpful in evaluating efficacy and safety of an unknown product. Therefore it is essential to have some control in the studies. Therefore all possible efforts for controlling data should be encouraged. However, specific study designs should be discussed with regulators in the form of a scientific advice.
457-461	11	**Comment:** Due to the small patient population, open label trials with outcome measures approved by the regulator should be encouraged.	**Not accepted**. See comment above.

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458-459	3	Comment: Although the preferred option for confirmatory trials would be randomised, double-blind parallel and possibly placebo controlled, available patient numbers may make such designs problematic. Strong rational for deviation from such designs should be considered. **Proposed change:** the guideline should be changed to incorporate the above.	**Comment accepted.** Please refer to the answer above.
458 & 469-470	12	**Comment:** As a parent with 2 children with Duchenne, I find it hard to comprehend that a placebo controlled trial is required, for rare exon mutations when current phase II trials are showing stabilization of boys after 84 weeks in the treated group and deterioration in placebo group. The stabilization is completely against the Natural History data published recently, based on standardized care and from an actual placebo arm of a phase 2b, international, multi center, randomized, double-blind, placebo-controlled, dose ranging study to evaluate the efficacy and safety of a therapeutic compound called ataluren: (**THE 6-minute walk test and other endpoints in Duchenne muscular dystrophy: Longitudinal natural history observations over 48 weeks from a multicenter study – June 2013**) It is infeasible to have randomized controlled trials for rarer exons and still have a group large enough to power the trial. It would seem unethical to have a trial approved for one exon skipping compound based on a	**Partly accepted**. See comment above.

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		surrogate endpoint, and then required a placebo in the next compound trial instead of comparing against the surrogate endpoint. **Proposed change:** Acknowledgement that the disease progression in Duchenne is consistent in natural history studies and that proof of dystrophin as a surrogate marker that shows stabilization in one cohort of duchenne patients, must not require placebo control group in a similar control trial where the same surrogate is being used (i.e. only difference is the antisense within the compound for exon skipping trials and the surrogate is dystrophin production).	
469-470	3	**Comment:** While historically the statement that the use of historical controls is not considered appropriate, we believe that with current data of natural history cohorts, with essentially identical data on disease progression measurements, that this data provides a useful contemporaneous control group that can be used to supplement placebo controlled data, or substitute for placebo data when implementation of a placebo arm is not feasible and could lead to unrepresentative data. **Proposed change:** Historic control data may be considered appropriate if it can be substantiated that the historic control information is contemporaneous to the patient population being compared to.	**Partly accepted**. See comment above. The paragraph will be corrected as follows: *"Generally, the use of historical controls is not considered an ideal approach due to a huge variability in patient populations, standard of care and co-medication during various times and treatment centres. The use of recent natural history cohorts[37] could be an option for small patient populations with a very rare genetic defect in which controlled studies are not feasible and if the use of such controls can provide an adequate comparison. However, it should be motivated what would generate the most evidence: a small placebo controlled trial with a type I error increased to reflect the rareness of the disease or a single arm trial with a justification that comparison with historical controls can be adequate."*

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469-470	5	**Comment:** We consider that the use of historical controls may be appropriate in some circumstances, for example, if it was possible to match patients with those for whom historical control data is available, *ie* same mutation/age/disease stage. In addition, for the rarer DMD mutations, placebo controlled studies may not be feasible and so historical control data will be useful. **Proposed change:** The use of historical controls is generally not recommended~~not considered appropriate~~ due to a huge variability in patient populations, standard of care and co-medication in various times and treatment centres. However, in certain cases it may be necessary to use historical data, for example, for rarer DMD mutations when placebo controlled studies may not be feasible and when it is possible to match patients with those for whom historical control data is available, *ie* same mutation/age/disease stage.	**Partly accepted.** See comment above.
470-471	1	**Comment:** We agree with this statement, but at the same time we propose the value of available datasets of current natural history cohorts, with essentially identical data on disease progression measures from the USA, Belgium, UK and Italy, as an example, given that they have been treated under the same standards of care as patients in clinical trials. **Proposed change:** To include the following statement: The use of natural history data will likely make the use of historic data a valuable means to contextualise the data seen in treated patients, particularly in long-term treatments where one can't utilise placebo. In that setting it is crucial to be able to	**Partly accepted**. See comment above.

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		use these data as the best means available to contextualise the findings.	
470-471	4	Comment: This statement should reflect current status. Use of previous historical natural history data sets are not appropriate given the improvements in patient care. However, recent publications from the EU and USA have provided evidence that with similar standards of care in place, disease progression was found to be very similar (Goemans et al., 2013, in press; MacDonald et al., 2013, in press). Similarities in patient care between these natural history studies and in current clinical trials suggest control data may provide significant value.	**Accepted**. See comment above.
471-508	2	**Comment:** the study duration and sample sizes should not be prescriptive for the same reasons of available patient population sizes.	**Accepted.** Paragraph has been modified according to this comment.
471-508	11	**Comment:** the study duration and sample sizes should not be prescriptive for the same reasons of available patient population sizes.	See comment above.
533	5	**Comment:** Transaminases are well-known to be very abnormal in boys/men with dystrophin mutations and muscular dystrophies in general. Cytosolic enzymes, such as CK, leak out of dystrophin-deficient fibers, therefore transaminases may also be elevated on hepatic screening. Unfortunately, there are reported cases of boys/men with dystrophin mutations that have received liver biopsies to evaluate for liver pathology when transaminases were elevated. Further, extremely high CK and transaminases are	**Partly accepted.** Hepatic adverse reactions have been included with modified wording: "*Special attention should be paid to hepatic safety; transaminases are known to be abnormal in patients with dystrophin mutations and muscular dystrophies in general, so liver toxicity due to treatment should be distinguished from this background elevation of liver enzymes."*

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		linked to rhabdomyolysis which can threaten acute renal failure. Therefore, we recommend that this Guidance should include a statement related to routine pharmacovigilance to assess for hepatic safety. **Proposed change: Endocrinological adverse reactions:** Special attention should be paid to weight gain and growth (retardation) in children. Distinction should be made between the effect of corticosteroid therapy and the test therapy. Depending on the pharmacological properties of the new therapeutic agent, the investigation of neuroendocrinological parameters (e.g. delayed puberty) may be necessary over an adequate period of time. **Hepatic adverse reactions:** Transaminases are known to be abnormal in boys and men with dystrophin mutations and muscular dystrophies in general. Hepatic safety should be monitored as part of routine pharmacovigilance.	
554	1	**Comment:** Another reason cardiac function may be more impaired after treatment is that muscle function improves so the strain on the heart becomes higher. It is also important to highlight and acknowledge that we do have mainstream therapies for cardiomyopathy and these are quite effective. **Proposed change:** Add the comment “this is also	**Not accepted** as this is a regulatory guideline.

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		discussed in Aartsma-Rus et al, Neuromuscular Disorders, 2013”	