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Workshop report

Report on the 124th ENMC International Workshop. Treatment of Duchenne muscular dystrophy; defining the gold standards of management in the use of corticosteroids 2–4 April 2004, Naarden, The Netherlands

K. Bushby^{a,*}, F. Muntoni^b, A. Urtizbarea^c, R. Hughes^d, R. Griggs^e

^a*Institute of Human Genetics, International Centre for Life, Central Parkway, Newcastle upon Tyne NE3 4YQ, UK*

^b*Hammersmith Hospital, Imperial College, London W12 0NN, UK*

^c*Institute de Myologie, 75013 Paris, France*

^d*Department of Clinical Neurosciences, Guys Hospital, London SE1 1UL, UK*

^e*University of Rochester Medical Centre, New York, NY 14642, USA*

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1. Introduction

Thirty-two participants representing parents, funding agencies and clinicians involved in the care of children with Duchenne Muscular Dystrophy (DMD) from Belgium, Canada, Denmark, Finland, France, Germany, Italy, the Netherlands, Spain, Sweden, the UK and the USA met in Naarden on 2–4th April 2004. The meeting was held under the auspices of the ENMC Clinical Trials Network, and with the additional support of the United Parent Project. The aims of the workshop were to define the need for clinical trials in DMD and develop a protocol for such trials, relating primarily to the use of steroids (prednisolone, prednisone and deflazacort) in DMD.

The first part of the meeting summarised the current state of practice on the use of steroids in DMD. Elizabeth Vroom (Netherlands) and Pat Furlong (USA) presented the views of parents surveyed by questionnaire by the United Parent Project. A major worry for parents was the lack of use of steroids at all in some countries, the multiplicity of steroid regimes used and the problems of getting firm information about which type of steroid or which regime for using steroids was best. This was reflected in the variation in practice amongst the participants at the Workshop, who

between them used at least seven different regimes for giving steroids, and some did not use steroids at all.

Adnan Manzur (UK), co-author of the Cochrane report on the use of glucocorticosteroids in DMD described the major findings of this systematic review [1]. Only five randomised controlled trials of the use of steroids in DMD were published in sufficient detail to be able to be included in the review. These trials did, however, present evidence that use of daily prednisolone (0.75 mg/kg per day) or deflazacort (0.9 mg/kg per day) increased strength in DMD. Robert Griggs, Richard Moxley (USA) and Doug Biggar (Canada) were able to confirm that long-term follow up of cohorts of patients treated under one or other of these regimes and who mostly continued using steroids beyond the loss of independent ambulation shows that this increase in strength is mirrored by improvement in function (with age at loss of ambulation in the mid teens, preservation of respiratory function, lack of need for scoliosis surgery and possibly preservation of cardiac function) [2–4]. With long-term use of steroids, the per kilogram dose of corticosteroid tended to reduce with time. In some cases, this was in response to side effects such as weight gain or behaviour changes, but in the majority represented a tendency not to keep up strictly with change in weight over time.

Many different regimes for giving steroids in DMD have been suggested as a way to reduce the risk of the well-known side effects associated with the long-term use of daily steroids. The dose of 0.75 mg/kg per day was shown to be

* Corresponding author. Tel.: +44-191-241-8757; fax: +44-191-241-8799.

E-mail address: kate.bushby@ncl.ac.uk (K. Bushby).

the most effective dose in the early randomised controlled trials, where dose response analysis showed that 0.35 mg/kg per day was not as effective as 0.75 mg/kg per day, while 1.2 mg/kg per day gave no additional benefit [5,6]. Deflazacort 0.9 mg/kg per day is said to be the equivalent dose to 0.75 mg/kg per day of prednisolone, and appears to be equally as effective [7,8]. Side effect profiles of the two regimes may differ slightly. Deflazacort appears to cause less weight gain, but is more likely to be associated with the development of asymptomatic cataracts. It is hard to assess the long-term differences in these regimes with respect to their effect on bone mineral density. Some studies have reported a high incidence of vertebral fractures with deflazacort, while other centres have not had this experience [2,9]. By far the most commonly reported side effects in the published series have been weight gain and behavioural changes [10].

There are known to be many other possible side effects of long-term daily steroid use. These include adrenal suppression, susceptibility to infection, hypertension, impaired glucose tolerance, gastrointestinal irritation and skin fragility. None of the centres with long-term experience in the use of steroids in DMD represented at the meeting had seen these complications at a high frequency.

Concern about side effects has led to the development of various regimes to minimise these risks. Some are based on the premise that intermittent dosing allows the body to recover from the effects of steroids by allowing a period off the drug (alternate day regimes, regimes using 10 days on steroids and 10 or 20 days off, or vice versa, weekend only regimes, etc.) with or without a reduction in the overall dose given [11–13]. Other regimes (daily low dosing) aim to reduce the cumulative steroid dose [14].

Proponents of all of these regimes describe benefit from their use, and a number of case or cohort reports are available, but no systematic studies have been published. Anneke van der Kooi (Netherlands) presented on behalf of her colleagues from Groningen (Beenakker et al) the results of the first randomised double-blind placebo-controlled crossover trial of an intermittent regime of prednisone (10 days on 0.75 mg/kg per day and 20 days off versus placebo during 6 months) [15]. This demonstrated that prednisone slowed deterioration of muscle function and force in ambulant DMD patients. Although side effects were present, the quality of life was not affected. Nathalie Goemans (Belgium) presented the plans of the CINRG group led by Diane Escolar (USA) to test weekend high-dose prednisolone against daily prednisolone for 1 year. A trial is under way in Germany (presented by Rudolph Korinthenberg) under the auspices of the MD-NET to test the effect of adding cyclosporin A to an intermittent (10 days on/10 days off) regime of 0.75 mg/kg per day prednisolone.

Despite the multiplicity of steroid regimes that have been devised and are in use across the world, none has to date been tested systematically against daily steroids at the proven effective dose to look at difference or equivalence of efficacy and the difference in rate of significant side effects.

Without this information, patients are being advised on steroid dosages without evidence-based facts as to the likely outcomes, based usually on personal experience of the advising physician. As it can now be concluded that the long-term use of daily steroids, introduced when patients are still ambulant and before they have lost major function, alters the natural history of the disease, the issue of ensuring that children are receiving an adequate dose becomes more imperative. It was decided therefore that the key hypothesis for development of a trial protocol should be that alternative regimes to daily steroids have a similar level of efficacy but a different side effect profile. After much discussion, it was agreed that the trial should test 0.75 mg/kg per day of prednisolone administered in a 10 days on/10 days off regime against 0.75 mg/kg per day. Additional arms of the trial (if sufficient patient numbers were available) would look at 0.9 mg/kg per day of deflazacort and 0.5 mg/kg per day of prednisolone.

Tony Swan (UK) summarised the statistical considerations involved in designing such a trial. Primary outcomes relating to function and side effects will need to be chosen to have the power to identify equivalence of effect and difference in side effects. This will require analysis of the likely variance in any of the likely measures chosen.

Small group discussions on the second day of the workshop addressed the design of the protocol in more detail, relating to the collection of outcome data and to the definition, management and prophylaxis of adverse events. A key aim for these discussions was to arrive at protocols that would be as simple as possible and allow for uniform data collection for the optimal management of children with DMD treated with steroids within or outside the context of a trial. Consideration was given to agreed protocols already in use such as the Utah dystrophinopathy project (<http://dystrophy.genetics.utah.edu/>) the German MD-NET (www.md-net.org) and the Scandinavian reference programme for DMD so that additional work for busy clinics could be avoided as much as possible. As only a minority of children with DMD will by definition be enrolled in a trial, it was also intended that the protocols used would be relevant to routine follow up and provide a framework for the care of any child with DMD using steroids. The parent representatives at the meeting emphasised the value of agreeing to collect long-term follow up data as well as collect data strictly within a trial, and this was also a focus of a small discussion group (see below). These protocols will be available through the ENMC website (www.enmc.org).

In the second part of the workshop, the meeting split to allow small groups to discuss development of specific areas of a trial protocol.

2. Session 1. Functional outcome measures

Michelle Eagle (UK) and Birgit Steffensen (Denmark) led a group discussing the kinds of functional outcome

Table 1
Suggested procedures for monitoring for efficacy of steroid treatment

Effect	Measure	Frequency	Adaptation for long-term follow up
Function (1)	Milestones of disease progression—can do, age lost (hop, jump, get up from floor, stand on one leg, step up, step down, walk, stand)	0,3,6,12 months, etc....	Needs no adaptation. Can be gathered by history and observation at long-term follow up and has high clinical relevance
Function (2)	Timed testing (time to get up from floor, to run defined distance)	0,3,6,12 months, etc....	Timed tests will become impossible as milestones of disease progression are reached
Function (3)	Hammersmith motor ability score	0,3,6,12 months, etc....	Scale may be less sensitive as children become less ambulant. May need adaptation or additional scale to accommodate changes in upper limb function
Muscle strength (1)	MRC score 34 muscle groups	0,3,6,12 months, etc....	Applicability may be limited in long term
Muscle strength (2)	Quantitative muscle testing six muscle groups, Citec dynamometer http://www.citec.nu/frm/uk.htm	0,3,6,12 months, etc....	Grip strength may remain useful measure in long-term follow up
Respiratory capacity	Forced vital capacity	0,3,6,12 months, etc....	Will need additional respiratory investigation as FVC drops
Cardiac status	Echocardiography, electrocardiology	0,12 months, etc....	Will need to be continued in long term as part of best practise monitoring [20]
Quality of life	CHQ–PF50, CHQ–CF87	0,3,6,12 months, etc....	Annual administration in long term

measures relevant to DMD. The ideal functional outcome measures would reflect real issues relevant to the disease, be simple to administer and to standardise across different evaluators, and be validated in previous studies. The conclusions of this session are summarised in Table 1.

Measures of function can be considered as three main groups.

2.1. Milestones of disease progression

In some ways these are the most useful and clinically meaningful ways to measure changes in function from one regime to another—e.g. comparing age at loss of ability to rise from the floor, age at loss of ambulation, etc. However, such outcomes for a trial would require very long-term follow up, especially if the children were to be recruited from a young age. A complementary approach would be to use an extended list of milestones—for example hopping (achieved by about 10% of DMD boys on steroids), jumping (achieved by about 50% of boys on steroids), getting up from the floor, standing on one leg, climbing up a step, climbing down a step, walking and standing.

2.2. Timed testing

Many clinics use timed tests as a measure of progression. Commonly used measures include time to rise from the floor (Gower's manoeuvre), time to run a set distance or time to climb a set of stairs. These are simple and reproducible tests, providing advice on how to perform the tests is standardised and the activities timed truly the same (same distance, standard steps, rising from sitting or lying, etc.).

2.3. Composite scores of function

Various composite scores of function have been defined which look at not only the time or actual ability to perform

an activity, but also the quality of the way the activity is performed. These include the Hammersmith motor ability score (HMAS) [16], the GSGC (gait, stairs, gowers, chair) score, and the EK score which is validated for the assessment of children in DMD after loss of independent ambulation [17,18]. A new score of motor function has recently been developed by Dr Carole Berard.

3. Session 2. Strength outcome measures

Michelle Eagle and Birgit Steffensen also co-ordinated the discussion on outcome measures related to changes in muscle strength. The main debate was around the use of manual muscle testing (used in most previous trials in DMD) or quantitative muscle testing (as validated by the CINRG group [19]), and about how many muscles to test. The issue of testing respiratory muscle strength was also discussed. The outcome of these discussions is summarised in Table 1.

3.1. Manual muscle testing

Many previous studies of steroids in DMD have used manual muscle testing (MMT) as the primary outcome measure, and a number of national networks of muscle clinics are using MMT in a selection of muscle groups (commonly 34) routinely to follow their patients. MMT is relatively quick and easy to do, but needs careful validation amongst practitioners to ensure reproducibility in a multi-centre setting. Different grading scales according to modifications of the MRC scale have also been devised.

3.2. Quantitative muscle testing

Myometry offers an alternative to manual strength testing, and the CINRG group suggests that it improves reliability in trials of DMD children. This requires all

centres to have the same equipment and standardised training. It was suggested that muscle strength of knee and elbow flexors and extensors, wrist extensors and grip were tested in the dominant side.

3.3. Respiratory muscle testing

Measurement of forced vital capacity and peak cough flow using the same equipment and technique was agreed to offer the best testing in ambulant children, with referral for pulse oximetry/further respiratory assessment if FVC was falling, according to good clinical practice. Again, centres must have standardised equipment to avoid problems with differences in machine calibration.

4. Session 3. Quality of life and related issues

Francesco Muntoni (UK) and Michael Rose (UK) led the session on quality of life (QOL) assessment, measurement of behavioural changes and caregiver burden. No long-term studies have systematically looked into these issues in children with DMD, and specific measures for this disorder are not available. Nonetheless, it was agreed that any long-term trial of steroid regimes should incorporate at least a generic measure or measures of QOL with separate child and parents questionnaires. The ideal instrument would be already validated and applicable to the age range we are interested in (down to 4–5 years), and practical to use that can be filled by parents and children with minimal or no supervision. A further requirement would be to be able to use an instrument already validated in different languages and socio-cultural backgrounds. In addition, if a muscle specific instrument was to become available, it would be of extra benefit to use this in parallel. Such instruments are currently under development in the USA and in Italy. Monitoring of behaviour would be important not only as a part of the general idea of quality of life, but also from the specific perspective that use of steroids in DMD is frequently reported to cause behaviour change and that some way to quantify this and assess its significance as a potential adverse effect would be an advantage.

The conclusion of the discussion was that the best instrument was probably the generic QOL measure, CHQ-PF 50/CHQ-CF87. This has been validated and implemented in most countries and different socio-economic-cultural backgrounds. It has a child and parent arm. It is widely used for physically disabling conditions and is validated in the age range we are interested in (5 years onwards). It has the additional benefit of including a large number of specifically behaviour-related questions, which could allow assessment of any impact on behaviour specifically.

Areas of further research include the need to compare the generic measures of QOL with the specifically neuromuscular scales currently under development. This could be done as a satellite initiative to the main trial. Further work

on this area is indicated and could impact on other paediatric neuromuscular disorders. In addition, measures for such important issues such as caregiver burden and health economics currently do not exist in this group of children. It was suggested that these could be addressed through a specific ENMC workshop on this topic.

5. Session 4. Implications for cardiology

John Bourke (UK), Giovanni Nigro (Italy) and Denis Duboc (France) led a session on cardiological issues. As cardiomyopathy is an almost universal finding in DMD, the effect of steroid treatment in this group on cardiac function will be important to consider [20]. Long-term cohort studies of boys treated with daily deflazacort suggest that there may be a cardioprotective effect of steroids [3], and no-one had any data to suggest that steroid treatment was detrimental to heart function. In the context of a trial of steroid treatment, the group recommended that cardiac function should be assessed on an annual basis preferably over a long period using electrocardiography and echocardiography. Management of any deterioration in cardiac function should be as already described with ACE inhibition and beta blockade [20].

Alongside the main steroid trial, possibilities for a trial of cardioprotection in DMD were discussed. Denis Duboc described the findings of a trial in which young boys with DMD had been treated with perindopril before the development of any signs of left ventricular dysfunction. The drug was well tolerated and after 5 years follow up, a smaller proportion of the treated boys had left ventricular dysfunction than of the placebo group. John Bourke presented a protocol for a study of combined ACE inhibition and beta blockade. It was agreed that such studies should be performed alongside the trial of different steroid regimes.

6. Session 5. Monitoring for side effects

The discussions on side effects were split into three groups. The conclusions of these discussions are presented in Table 2.

6.1. Weight and height

The group discussing weight and height was led by Doug Biggar (Canada) and Adnan Manzur (UK). Weight gain is the most frequently reported side effect for children with DMD treated with steroids. In a large German trial of prednisolone versus deflazacort, 10% dropped out of the trial protocol because of weight gain, and dropouts were seen with both drugs, though on average deflazacort may be associated with less weight gain than prednisolone. In the Dutch trial of intermittent prednisolone, 60% of the treated group had weight gain and 30% of the untreated group. Hence, the problems are compounded by the fact that many

Table 2
Adverse event monitoring and responses

Adverse event group	Measure	Prophylactic measures	Events to be recorded/treated without dose alteration	Events as criterion for dose reduction	Events as criterion for drug withdrawal	Long-term monitoring
Behaviour changes	CHQ–PF50, CHQ–CF87	Advice on behaviour modification	Change in behaviour from baseline. Psychology input as necessary	Behaviour changes disrupting family/school life	Severe behaviour changes disrupting family/school life	As for QOL issues
Weight	Weight for age/height/BMI 0,3,6, 12 ... months, etc.	Dietary advice	Change in weight centile from baseline. Reinforced dietetic input as necessary	25% or 3 centile increase from baseline	Weight gain unacceptable to child/family despite dietetic input/dose reduction	Continue annually in long term
Height	Standing height or arm span in non ambulatory children 0,3,6, 12... months, etc.		Change in height compared to predicted centiles	Failure to gain height that is unacceptable to child/family	Failure to gain height that is unacceptable to child/family despite dose reduction	Arm span necessary for assessment of respiratory function in non-ambulant patients
BD	DEXA baseline and annually, recording of fracture history 0,3,6 ... months, etc.	Vit D, calcium dietary advice, sunshine, exercise	Fracture, site, trauma. Limb fracture to be treated with early mobilisation. Vertebral fracture to be treated with iv bisphosphonates			Long-term risk of vertebral fractures needs to be addressed by history. Careful checking of X rays obtained for other reasons for vertebral fracture
Glucose tolerance	Blood, urine glucose 0,3,6, 12... months	Dietary advice		fasting blood sugar > 110 < 126 mg/dl after dietary modification or blood glucose two hours after meal > 140 < 200 mg/dl	Diabetes mellitus as defined as fasting blood sugar > 126 mg/dl or blood glucose 2 hours after a meal < 200 mg/dl	Urinalysis
Blood pressure	Blood pressure compared to age norms, measured 0,3,6, 12... months	Advice about dietary sodium intake		Consistent increase in systolic blood pressure 15 mmHg over the 97th centile or diastolic blood pressure of 10 mmHg over 97th centile for age after sodium restriction	Confirmed hypertension as defined as an increase in systolic blood pressure of 15–30 mmHg over the 97th centile or diastolic blood pressure increased 10–30 mmHg over 97th centile for height	
Immune/adrenal suppression	History of infection. Measure adrenal axis at start, midpoint and end of trial	Ensure prior exposure/immunisation to chicken pox. Advise on steroid cover for surgery/injury	Infectious diseases. Abnormal response to stress	Unusually high frequency of infection/unusual organisms—seek guidance from immunology expert		
Gastro intestinal symptoms	History 0,3,6, 12 ... months, etc.	Advise to avoid NSAIDs	Abdominal pain/peptic ulceration—treat with gaviscon, zantac	Persistent GI symptoms despite treatment		History, also history for other GI symptoms in long term, e.g. constipation
Cataract	Ophthalmology/visual acuity examination yearly for cataracts and intraocular pressure		Cataracts— if symptomatic, surgery. Increased IOP—follow ophthalmological advice			Visual acuity assessment
Skin changes	History and examination at 0,3,6,12 ... months for atrophy, easy bruising, fragility, striae, cutaneous/oral infections		Skin changes, type and extent. Treat infections as indicated			

children with DMD gain excessive weight even in the absence of steroid treatment, a tendency probably accentuated because of their relative lack of activity. In itself, excessive weight can cause reduced mobility as well, so careful control of this factor is clearly of major importance.

For any child with DMD therefore it is important to document weight, and for a trial of steroids where difference in side effects of different regimes is one of the primary end points, a clear definition of when weight gain becomes a substantial adverse event is of primary importance. It is not clear if this is best related to age or to height (by the use of weight for height charts or the calculation of body mass index).

An absolutely essential adjunct to any trial or any protocol of monitoring of steroid use in DMD is dietary advice, preferably from an experienced paediatric dietician, but supplemented with written patient and parent information. This should include the need to cut down on high calorie foods and maintain a healthy diet. Parents should be warned that appetite can increase dramatically at the onset of steroid use, and to be aware of that and ready to control appetite at that stage if possible.

Long-term use of daily steroids also has an effect on linear growth. Doug Biggar (Canada) observes that in his cohort of teenage boys treated over long periods with daily deflazacort, there is loss of final adult height, but that this appears to confer an additional advantage on muscle strength. There has never been systematic study of the feelings of the boys in whom height is limited as to whether they see this as an acceptable pay off for their improved mobility.

6.2. Bone mineral density

Doug Biggar and Nathalie Goemans (Belgium) led the group discussing bone mineral density (BD). BD is typically reduced in boys with DMD even before steroid use, and is associated with an increased risk of limb fractures [21]. This probably relates to relatively low levels of activity, though recent studies also show that children with DMD may have abnormally low levels of vitamin D even at diagnosis [22]. Vertebral fractures are rarely seen in people with DMD who are not treated with steroids. Studies of bone mineral density in DMD show that vertebral bone density decreases once boys are using a wheelchair, and vertebral fractures have been reported in boys treated with steroids [23]. In one study where daily deflazacort was used, the incidence of vertebral fractures was as high as 44% [9].

There is therefore a high level of concern about the prevention and treatment of decreasing bone mineral density in steroid treated DMD. Unfortunately, although several techniques exist to measure bone mineral density, there are problems with the interpretation of the results, (especially in paediatric practice where standardisation may

be difficult to achieve) and specifically the interpretation of what a single finding might mean to an individual patient. No absolute figures can be used to predict risk of fracture.

Amongst the participants at the workshop, practice relating to prophylaxis and treatment of problems with bone density varied considerably. Several gave calcium and vitamin D supplementation, and some used oral bisphosphonates. Francesco Muntoni and Kate Bushby discussed the outcomes and recommendations of a recent workshop on a similar topic held in the UK. Here, it was emphasised that dietary calcium and vitamin D were more effective at improving BD than supplements, hence that dietary advice was crucial. Promoting exercise is another good way to maintain or improve BD. Experience in other conditions where low BD is an integral part of the phenotype have indicated that in experienced hands, iv bisphosphonates are a good treatment for vertebral fracture or bone pain caused by micro fractures in patients with low BD. Oral bisphosphonates are not currently licensed for use in children and there is to date currently little published evidence of their efficacy in childhood.

Francesco Muntoni presented data on children using the 0.75 mg/kg prednisolone 10 days on/10 days off regime who over many years did not have deterioration of BD. Doug Biggar presented an open label study of oral bisphosphonates in DMD, with good tolerance of the drug. It appeared that ambulant children responded better than those who had lost ambulation.

The recommendations of the group therefore were that in the context of a trial DEXA scans at initiation of treatment and at yearly intervals were indicated to monitor trends between the different treatment arms but results of DEXA scans should not in themselves trigger any change in treatment or withdrawal as an adverse effect and that standardisation of measurement was essential. Dietary advice is mandatory and exercise and sunshine should be promoted. Vitamin D levels should be tested at onset of treatment and any deficiency corrected. Limb fractures should be treated with early mobilisation and their frequency and associated trauma should be recorded. Any vertebral fractures should be recorded as traumatic or non traumatic and treated in consultation with a bone expert by iv bisphosphonates.

Meantime, there is an urgent need to look at the role of oral bisphosphonates in prophylaxis against loss of BD in children treated with long-term corticosteroids. This and other issues relating to the development and treatment of BD problems in DMD and other neuromuscular disorders will be addressed in further trials and via another workshop.

6.3. Other side effects

A group led by Nathalie Goemans (Belgium) and Jaume Colomer (Spain) discussed other side effects of corticosteroid treatment. A well-known side effect of steroids is

impaired carbohydrate tolerance. Base line measurements should include blood and urine glucose testing, and monitoring by testing for glycosuria. Dietary modification should be promoted to increase the proportion of complex carbohydrates, reduce intake of simple sugars and spread food intake out over the day. Glucose intolerance as defined as fasting blood sugar >110 mg/dl <126 mg/dl after dietary modification or blood glucose 2 h after meal >140 <200 mg/dl would be indications for dose reduction and reported as such. Diabetes mellitus as defined as fasting blood sugar >126 mg/dl or blood glucose 2 h after a meal >200 mg/dl would be an indication for withdrawal.

There is less chance of hypertension with the steroids used in this trial than with those with more mineralocorticoid activity. Blood pressure monitoring should be performed with criteria for dose reduction of increase in systolic blood pressure 15 mmHg over the 97th centile or diastolic blood pressure of 10 mmHg over 97th centile for age after sodium restriction. Confirmed hypertension as defined as an increase in systolic blood pressure of 15–30 mmHg over the 97th centile or diastolic blood pressure increased 10–30 mmHg over 97th centile for height would be a criterion for withdrawal.

Gastrointestinal side effects have rarely been reported in steroid-treated DMD. Some centres choose to use adjunctive medications such as TUMS or gaviscon to try and prevent GI upset. Assessment of such issues is by history and treatment by gaviscon (for minor disturbance) or medication such as ranitidine if symptoms are not responsive to gaviscon.

Ophthalmological examination is for the two reported side effects of corticosteroid treatment, cataracts (reported only in deflazacort treated children) and increased intra-ocular pressure. To date, cataracts in children with DMD treated with deflazacort have not been symptomatic and none have required treatment.

Despite many years of treatment with steroids in DMD, there are few reports of serious immunosuppression. Children should have had chicken pox or chicken pox immunisation prior to starting steroids. It is currently recommended that it is safe to use live vaccines in children treated with less than 2 mg/kg per day of prednisolone.

7. Session 6. Long-term monitoring

It was the unanimous decision of the meeting that a long-term follow up strategy was essential and that assessments should be made as simple as possible to reflect this need. Functional measures, and in particular noting of milestones of disease progression are essential in this context. Apart from the measures already noted, monitoring of development of respiratory failure and the need for nocturnal ventilation, and the development and need for treatment of scoliosis would be additional needs in the longer term follow up group. There was, within the group, some discussion

about the need for a long-term controlled trial (8–10 years) and the possibility of a 3 year long trial followed by 5–7 years follow up with open label treatment. Theoretically, all agreed that the first design would be preferable. The first design would be feasible if there was no clear difference in benefit between two regimens and if there were no clear differences in terms of side effects. The second design was considered the more practical one, with measures as non-invasive as possible, for example with avoidance of blood tests, monitoring of visual acuity rather than slit lamp examination, and the use of X rays obtained for other reasons such as scoliosis surveillance for evidence of fracture. The need for monitoring of gastrointestinal function in the context of long-term survival potentially unmasking a tendency to smooth muscle disease was also noted.

8. Session 7. Funding options

An important feature of this workshop was the participation of parent groups and various funding agencies (the Association Francaise contre les myopathies (AFM, France), Muscular Dystrophy Association (MDA, USA), United Parent Project, and Telethon (Italy)). Working together to fund multinational efforts such as this was recognised as the only viable option, and there was considerable support for this initiative. The group suggested that a planning application could be submitted to the NIH. The aim of the planning part of the trial would be to support the organisers of the trial and allow some meetings of the investigators to set up the trial and write a grant application for consideration by the US National Institutes of Health, the British Medical Research Council, and the muscular dystrophy charities themselves. Support could also be sought from other agencies such as from the MDA for funding of investigators' meetings, and the AFM for support for the planning stage and the trial itself. Other options could also exist, such as the individual partner countries departments of health.

9. Conclusions and workshop outcomes

1. It was agreed that the evidence for the use of daily steroids in DMD is now established and that trials of other treatments should be against this 'gold standard'.
2. Many measures can be put in place to monitor for, minimise or treat predictable side effects and these should be standardised as much as possible. Guidelines developed from this meeting will be available through the ENMC website and are summarised in [Table 2](#).
3. Patient information material is crucial and should be distributed through the patient and parent organisations, and also through the ENMC website.

4. There are many alternative steroid regimes in use in DMD without systematic evidence as to their efficacy or side effect profile compared to daily steroids. Hence, there continues to be polarisation of practice, and it is very difficult for families to get clear advice about the relative benefits of the different regimes on offer. Agreement was therefore reached that plans for a trial of different steroid regimes, to be run on an international basis, and supported by universally applicable monitoring protocols will be further developed. It would not be appropriate, however, for treatment with steroids in children who could potentially benefit to be withheld in advance of such a trial.
5. Alongside the major hypothesis, trials of cardiac and bone protection will also be planned, as well as the issue of possible benefit in starting steroids in young people with DMD after the loss of ambulation.
6. There are areas where further attention needs to be paid to development of more specific outcome measures, especially in the area of quality of life.

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Appendix. List of workshop participants:

Dr Anna Ambrosini (Telethon, Italy),
 Dr Anne d'Andon (AFM, France),
 Prof. Corrado Angelini (Italy),
 Dr Carole Bérard (France),
 Dr Enrico Bertini (ENMC observer, Italy),
 Dr Doug Biggar (Canada),
 Dr John Bourke (United Kingdom),
 Dr Jaume Colomer (Spain),
 Prof. Denis Duboc (France),
 Prof. Victor Dubowitz (ENMC observer, United Kingdom),
 Dr Michelle Eagle (United Kingdom),

Prof. Brigitte Estournet (France),
 Dr Kevin Flanigan (USA),
 Dr Patricia Furlong (USA),
 Dr Nathalie Goemans (Belgium),
 Dr Imelda de Groot (The Netherlands),
 Dr Sharon Hesterlee (MDA, USA),
 Dr Anneke van der Kooi (The Netherlands),
 Prof. Rudolf Korinthenberg (Germany),
 Dr Adnan Manzur (United Kingdom),
 Dr Richard Moxley (USA),
 Prof. Giovanni Nigro (Italy),
 Dr Helena Pihko (Finland),
 Dr Michael Rose (ENMC clinical trials network, United Kingdom),
 Dr Thomas Sejersen (Sweden),
 MS Birgit Steffensen (Denmark),
 Dr Tony Swan (ENMC clinical trials network, United Kingdom),
 Prof. Andoni Urtizberea (ENMC research director, France),
 Dr Marcello Villanova (Italy),
 MS Elizabeth Vroom (The Netherlands) and
 Dr Maggie Walter (Germany).

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