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# Moving beyond the 2018 minimum international care considerations for osteoporosis management in duchenne muscular dystrophy (DMD): Meeting report from the 3rd International Muscle-Bone Interactions Meeting 7th and 14th November 2022

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Meeting Report

# Moving Beyond the 2018 Minimum International Care Considerations for Osteoporosis Management in Duchenne Muscular Dystrophy (DMD): Meeting Report from the 3rd International Muscle-Bone Interactions Meeting 7th and 14th November 2022



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## INTRODUCTION

Individuals living with Duchenne muscular dystrophy (DMD) are at significant risk of bone fragility due to osteoporosis, with the most potent drivers of fragility fractures in this context stemming from the aggressive myopathy and long term oral glucocorticoid therapy. Young people with DMD have a high fracture burden, with reported total and vertebral fracture rates that are four [1, 2] and 535 times [1] higher than those of healthy growing boys, respectively. Vertebral fractures can occur as early as six months following daily glucocorticoid initiation [3]. Up to 75% of young people with DMD sustain at least one fracture after eight years of glucocorticoid therapy [4]. Fractures in DMD can lead to devastating outcomes, including steeper rates of functional decline, premature and permanent loss of ambulation, chronic pain, and even death from fat embolism syndrome or adrenal crisis following long bone fractures [2, 5–8]. The potential for serious consequences and medical complications linked to fractures has driven efforts to develop effective guidelines for timely bone health surveillance and treatment with more recent efforts to develop fracture prevention strategies.

To guide clinicians in the management of DMD and its related co-morbidities (including skeletal health), the first internationally-endorsed, minimum standards of care were published in 2010 under the moniker "Clinical Care Considerations" [9, 10]. This document recommends that osteoporosis monitoring include spine x-rays if back pain or kyphosis is present, followed by initiation of intravenous bisphosphonate therapy if vertebral fractures are identified [10]. In the years following the inaugural 2010 Clinical Care Considerations, studies were published showing that vertebral fractures, a key manifestation of bone fragility among children and adults living with glucorticoid-treated chronic conditions, were frequently asymptomatic, necessitating routine surveillance for early detection [3, 11]. It was also better appreciated that even a single long bone fracture can signal osteoporosis in a persistently high-risk setting such as DMD, and prompt initiation of bone protection therapy is important.

With this new knowledge, the latest international, minimum standards of clinical care for DMD published in 2018, known as Care Considerations [12–14], recommended routine, standardized spine imaging for early detection of vertebral fractures, combined with more timely bone-targeted (bisphosphonate) intervention in the presence of vertebral or low trauma long bone fractures [12]. At the same time, the ever-changing therapeutic landscape for the treatment of the underlying condition calls for ongoing examination of the intimate relationship between muscle and bone development in DMD, including the effect of different DMD treatment approaches on the skeletal and endocrine systems. The overall goal of such focus is to harvest discussions about optimal management that will foster bone strength and prevent fractures in this high-risk setting across all underlying disease-targeted treatment paradigms for people with DMD.

This current manuscript summarizes the proceedings of the "Third Muscle-bone interactions in Duchenne Muscular Dystrophy Symposium: Moving Beyond the 2018 Minimum International Standards of Care for Osteoporosis Management", an event co-organized by the World Duchenne Organization (www.worldduchenne.org) and the International Conference on Children's Bone Health (www.theiscbh.org). This virtual symposium, held on November 7th and 14th 2022, brought together a total of 385 delegates representing 55 countries registered for the symposium, which included 239 clinicians, 70 researchers, 40 patient representatives and others from pharmaceutical companies and regulators. This symposium aimed to review the evidence base that informed the 2018 international minimum Care Considerations, best practices for implementation of

these Care Considerations, and emerging knowledge that has arisen from research since the 2018 Care Considerations that shines light on the path forward. The online symposium and this report cover the following areas:

1. Current understanding of the bone morbidity in DMD, especially in relation to conventional glucocorticoid therapy.
2. The published, 2018 minimum international Care Considerations for osteoporosis monitoring and management in DMD [12].
3. Real world initiatives and challenges in the implementation of the 2018 minimum international Care Considerations for osteoporosis monitoring and management in DMD.
4. The need to consider strategies to move beyond the 2018 minimum international Care Considerations to prevent first fractures in DMD.
5. New therapies in DMD with potential impact on skeletal outcomes.

## UP TO DATE UNDERSTANDING OF BONE FRAGILITY IN DMD AND CONVENTIONAL GLUCOCORTICOID REGIMEN

### *Results from the FOR-DMD clinical trial*

Drs. Michela Guglieri (Newcastle, United Kingdom) and Leanne Ward (Ottawa, Canada) presented the muscle-bone and endocrine outcomes from the Finding the Optimal Regimen (FOR)-DMD clinical trial (clinicaltrials.gov NCT01603407). Oral glucocorticoid (prednisone/prednisolone and deflazacort) are part of care considerations of management in DMD [13]. Although their benefits are well established [15, 16], there is still uncertainty regarding the optimal glucocorticoid regimen and dosage. This has led to variability in glucocorticoid prescription in DMD that may affect clinical care and health outcomes [15–17].

Dr. Guglieri discussed the FOR-DMD study results of skeletal muscle outcomes. FOR-DMD is a randomized, double-blind, parallel-group clinical trial comparing benefits and side effects of the three most commonly prescribed glucocorticoid regimens in boys with DMD in the international sphere: daily prednisone (0.75 mg/kg), daily deflazacort (0.9 mg/kg), and intermittent prednisone (0.75 mg/kg 10 days on/10 days off) [18, 19]. In total, 196 glucocorticoid-naïve boys with genetically-confirmed DMD were enrolled in the study at 32 sites in five countries. The mean age ± standard deviation (SD) at randomization was 5.8 ± 1.0 years and boys were evaluated for three years. Daily prednisone and daily deflazacort were superior to 10 days on/10 days off prednisone for all motor function outcomes, including the North Star Ambulatory Assessment, the time to rise from the floor, the time to run/walk 10 meters, and the 6-minute walking tests [18]. There were no significant differences in efficacy between daily prednisone and daily deflazacort. There was greater weight gain with both daily and 10 days on/10 days off prednisone when compared with daily deflazacort. Slowing of growth was less severe with the 10 days on/10 days off prednisolone than with the daily regimens, with daily deflazacort associated with the greatest growth attenuation [18]. The results of the FOR-DMD study support the use of a daily glucocorticoid (prednisone or deflazacort) regimen over the 10 days on/10 days off prednisone regimen as initial treatment for muscle strength preservation among boys with DMD.

Dr. Ward reviewed emerging vertebral fracture data from the FOR-DMD study carried out by The Ottawa Pediatric Bone Health Research Group after 36 months of glucocorticoid exposure. Lateral spine radiographs were evaluated according to the Genant semi-quantitative method according to a triple read protocol by certified pediatric radiologists in active clinical practice. Eighty-two boys participated in the FOR-DMD vertebral fracture prevalence sub-study. The vertebral fracture prevalences at 36 months were as follows: 8/28 boys on daily deflazacort (29%), 7/27 boys on daily prednisone (26%) and 0/27 boys on 10 days on/10 days off prednisone. All fractures were mild (Genant grade 1) with the exception of one patient who had a single, Genant grade 2 fracture on daily deflazacort. The Spinal Deformity Index (sum of the Genant grades and therefore a marker of overall spine fracture burden) was highest on daily deflazacort. Interestingly, these results were in line with the ordinal ranking of classic glucocorticoid in relationship to fracture frequencies described by Dr. Jarod Wong's group [1]. In the study of boys enrolled in the UK North Star study by Dr. Wong's group, Joseph et al. showed that clinical symptomatic fractures (all types i.e. long bone fractures and symptomatic vertebral fractures) were highest in patients on daily deflazacort followed by daily prednisone, with fewer (but not absent) fractures on intermittent prednisone [1]. These data affirm that deflazacort, whilst associated with lesser weight gain

according to the FOR-DMD study [18], is not bone-sparing.

These results, combined with the FOR-DMD muscle function data corroborated an earlier theme put forward by Crabtree et al. [20] in a retrospective study that showed lower vertebral fracture burden on prednisolone 10 days on/10 days off compared with daily prednisolone, but at a cost to muscle strength. Together, the data presented by Drs. Guglieri and Ward provide valuable information for clinicians and families when making decisions about the choice of daily versus 10 days on/off glucocorticoid regimens.

*High dose weekend only glucocorticoid regimen in DMD*

Dr. Anne Connolly (Columbus, USA) reviewed high-dose weekend-only glucocorticoid therapy in DMD. Preclinical work in *mdx* and *dydy* mouse models showed that twice weekly oral prednisone at murine doses of 5 mg/kg/dose [21] or 0.01 mg/g/week [22] maintained muscle function and improved longevity. Twice weekly glucocorticoid (prednisone 10 mg/kg/week in two daily doses of 5 mg/kg each) was originally tested in boys with DMD to mitigate side effects of daily glucocorticoid (Cushingoid effects, short stature, fractures). The first open-label study in DMD boys (mean age $8.0 \pm 1.0$ years) included 20 consecutive boys undergoing care in a single academic practice who received twice weekly oral prednisone (5 mg/kg/dose) [23]. All 20 boys showed functional improvement over six months compared with baseline for upper extremity strength by dynamometer ($p = 0.001$), for grip strength ($p = 0.002$), and for proximal lower extremity strength by dynamometer ($p < 0.0001$). Maintenance of normal linear growth was observed in all those on twice weekly oral prednisone (5 mg/kg/dose). None developed Cushingoid features, hirsutism, acne, and hypertension. Fifteen of the 16 patients treated for an average of 22 months remained stronger than at baseline.

Subsequently, a 12-month randomized, double-blinded study of daily prednisone 0.75 mg/kg/day versus weekend-only prednisone 10 mg/kg/week was performed on 64 boys (mean age 7.3 years) [24]. The study showed similar efficacy for both regimens over 12 months for quantitative muscle testing arm score ($p < 0.0001$) and quantitative muscle testing leg score ($p = 0.02$). Height velocity increased over 12 months on twice weekly prednisolone compared to daily prednisolone (mean change over 12 months in the weekend versus daily dose groups, 6.6 vs 4.1 cm, $p = 0.002$). Lumbar spine (LS) bone mineral density (BMD) Z-scores were obtained by dual energy absorptiometry (DXA) in 26 boys from each treatment arm. LS BMD Z-score improved by +0.26 in the twice weekly group over one year compared with a decline of –0.30 in the daily cohort ($p = 0.001$). In another study, twice weekly prednisolone at the same doses in infants and young boys with DMD over 12 months also demonstrated improved short-term safety and efficacy relative to untreated boys [25, 26]. These encouraging short-term results with respect to comparable muscle strength efficacy and improved linear growth merit longer term study beyond one year. In addition, the relative efficacy of twice weekly therapy with respect to time to loss of ambulation, the incidence of scoliosis, cardiorespiratory function, and harm reduction including weight and fragility fractures, in comparison with daily glucocorticoid, require further study with a controlled trial design over the longer term.

## THE 2018 CARE CONSIDERATIONS FOR MANAGEMENT OF BONE FRAGILITY IN DMD

*Bone & endocrine morbidity in DMD with focus on the 2018 Care Considerations*

Dr. David Weber (Philadelphia, USA) reviewed the 2018 update to the DMD Care Considerations, which included an expanded section on bone health/osteoporosis and a new section on endocrine care [12–14]. The minimum standards set forth in the updated 2018 Care Considerations outline an approach for the "Monitoring and Diagnosis", "Treatment Stabilization", and "Treatment Maintenance" phases of osteoporosis. Anticipatory osteoporosis monitoring should begin no later than at the time of initiation of glucocorticoid. Clinical evaluations include fracture and dietary history, assessment for focal back pain, lateral spine imaging, DXA LS BMD, and biochemical assessment of 25-hydroxyvitamin D (25OHD). A key change from prior guidance (2010) is the prioritization of vertebral fracture assessments over BMD for clinical decision-making. In 2010, it was recommended that spine imaging be undertaken in the presence of back pain or kyphosis [9]. Between 2010 and 2018, a number of studies were published which highlighted that vertebral fractures are a key manifestation of osteoporosis

in children, and that they are frequently asymptomatic in their early phases (and even in the face of moderate and severe collapse) [11, 27]. Bone protective therapy with intravenous bisphosphonates at standard doses for stabilization should begin at first clinically significant vertebral (symptomatic vertebral fracture of any grade or > 25% compression i.e. Genant grade 2 or 3 even without back pain) or long bone fracture. Once clinical stability is achieved including absent new fractures and a normal rate of bone mineral accrual for age, sex and height, bisphosphonate therapy should be titrated as necessary (up or down) to maintain an appropriate bone mineral accrual rate. Vitamin D supplementation to maintain 25OHD > 50 nmol/L (20 ng/dl), calcium intake to achieve adequate intake for age [28], and testosterone therapy for hypogonadism after age 12–14 years should also be provided.

*An appraisal of the published literature on bone protective therapies in DMD recommended in the 2018 Care Considerations: Testosterone and Bisphosphonates*

Dr. Craig Munns (Brisbane, Australia) reviewed the published literature on testosterone and bisphosphonate therapy in DMD. The two primary medical interventions available to increase bone mass and potentially reduce fracture in growing young people with DMD are bisphosphonate therapy (a primary, bone-targeted approach) and testosterone (a primary, delayed puberty-targeted approach and an adjuvant bone-targeted strategy).

Long term oral glucocorticoid therapy is associated with delayed pubertal development in boys with DMD. Pubertal delay has been shown to increase fracture rates in adult males in the absence of DMD [29]. Lee et al. evaluated, in an uncontrolled observational study, the effect of oral and intramuscular testosterone on BMD in a cohort 16 adolescents with DMD aged 14–17.7 years who were already receiving intravenous bisphosphonates with zoledronic acid therapy for osteoporosis [30]. Their data showed that 33 months of testosterone was associated with a DXA LS BMD increase of 25.95% (+13.3% oral and +28.29% intramuscular testosterone). The relative contribution of zoledronic acid versus testosterone in relation to the percent changes in LS BMD were not distinguishable due to the study design. There were no reported side-effects to testosterone. In 14/16 boys, spine images before and after testosterone were available: 12 boys had stability of vertebral fractures and 2 boys had progression of vertebral fractures.

Wood and colleagues observed in a two-year prospective study of 15 pre-pubertal boys with DMD (of whom 12 were also on oral or intravenous bisphosphonates) that incremental monthly testosterone injections for pubertal induction appeared to stabilize DXA LS BMD [31]. There was, however, a wide variability in BMD trajectory among participants, with some showing decline, whilst others remained stable or increased. Their data additionally showed that muscle contractile cross-sectional area on magnetic resonance imaging remained stable after two years on intramuscular testosterone, suggesting that testosterone therapy did not adversely affect the muscles. However, the testosterone regimen did not rescue the muscle phenotype, as evidenced by declining Performance of Upper Limb and North Star Ambulatory Assessment scores consistent with changes from natural history studies [31]. Intramuscular testosterone was well tolerated and associated with high satisfaction [31]. All these studies provided supportive evidence for the clinical recommendation to treat delayed puberty with testosterone as outlined in the 2018 Care Considerations [13].

There have been two recent randomised controlled trials of 6 monthly intravenous zoledronic acid 0.05 mg/kg in boys with DMD [32, 33]. Both trials showed intravenous zoledronic acid was associated with significant increase in DXA LS BMD Z-scores. Ward et al. demonstrated a + 0.75 Z-score difference in the change from baseline to 12 months in height Z-score-adjusted LS BMD Z-score on zoledronic acid versus intravenous placebo, $p = 0.004$; 38% of participants with a diagnosis of DMD [32]. Zacharin et al. showed a +1.3 SD difference in the change over 24 months on zoledronic acid plus calcium + vitamin D supplementation versus calcium and vitamin D supplementation alone [33]. There were non-significant increases in total body BMD in both studies. Zacharin et al. also showed an increase in radial trabecular volumetric BMD on peripheral quantitative computed tomography on zoledronic acid plus nutritional support versus nutritional support alone [33]. Data from the Zacharin et al. study also suggested that zoledronic acid may have a role in preventing incident vertebral fractures, with 24% of control subjects developing incident vertebral fractures over the 24-month duration of the study compared to 15% in the zoledronic acid cohort. Further, five of 31 boys in the control arm withdrew from the study due to incident (new) grade 3 vertebral fractures compared to none

with severe incident vertebral fractures in the zoledronic acid cohort [33]. Ward et al. made a similar observation, since two patients in the placebo group had a single low-trauma vertebral fracture over the 12 months of observation, one of whom withdrew from the study due back pain [32].

There are several studies investigating the effect of oral bisphosphonates in boys with DMD [34–38], but to date there are no randomised controlled trials. Generally speaking, oral bisphosphonates have not gained traction in osteoporotic children due to the extremely low oral bioavailability in both primary [39] and secondary [40] pediatric osteoporosis settings, with corresponding failure of oral bisphosphonate therapy to achieve important endpoints in large, randomized controlled trials of alendronate [41] and risedronate [42] in osteogenesis imperfecta, and risedronate in glucocorticoid-induced osteoporosis [43]. In fact, vertebral fractures were more common in the risedronate-treated group compared with the placebo group in the osteogenesis imperfecta trial by Bishop et al. [42], an observation particularly important, since intravenous bisphosphonate therapy is highly effective in preventing vertebral fractures and reshaping vertebral bodies in pediatric osteogenesis imperfecta [44] and therefore failure to achieve this with oral risedronate in osteogenesis imperfecta underscores the reduced efficacy. In the same vein, serum bone resorption markers *increased* on risedronate in the study of children with GC-induced osteopenia and juvenile rheumatic disease [45]. Nasomyont et al. followed 52 boys with DMD on oral bisphosphonates (alendronate) for five years and showed that worsening of vertebral shape was observed in 28/52 (54%), with lack of worsening noted in 46% [38]. Among those with lack of worsening, 8/24 (33%) had complete vertebral body reshaping defined as return of normal vertebral body height. Tian et al. showed a statistically significant improvement in DXA LS areal and size-adjusted BMD Z-score on alendronate compared with pre-alendronate in a longitudinal observational study [37]. This improvement was maintained for three years before showing evidence of subsequent decline. In contrast, there was no improvement in DXA total body less head (TBLH) BMD Z-score, even in the short-term, on alendronate compared with pre-alendronate. In this uncontrolled study of 54 boys, 35% had new or worsening incident vertebral fractures over 5 years.

In line with the low bioavailability of oral bisphosphonates, there appears to be relatively fewer side effects compared with intravenous bisphosphonate therapy [37, 38]. In contrast, reported side effects of the more potent intravenous bisphosphonates in boys with DMD include the first infusion acute phase reaction (fever, nausea, bone pain), precipitation of adrenal crisis for those on chronic glucocorticoid therapy, hypocalcaemia and rarely rhabdomyolysis [32, 33, 46, 47]. There has been one report of bisphosphonate-related osteonecrosis of the jaw in a 26-year-old man with DMD who had received 11 years of oral alendronate [48]. Interestingly, this patient did not have a history of a dental extraction, but did have tongue hypotonia and difficulty clearing oral secretions. The oral lesion healed with a combination of antibiotics, mouthwash, and photodynamic therapy [48].

In 2011, Gordon et al. published an observational study of 44 boys with DMD, 16 of whom had received either oral or intravenous bisphosphonate [49]. Their data showed that oral or intravenous bisphosphonate was associated with an increased survival: 60% of boys treated with a bisphosphonate were alive at 24 years of age, whereas 60% of boys not treated with a bisphosphonate were alive at 16 years of age. The reason for the observation is still unclear but could relate to improvement in respiratory function due to improved spine anatomy, or preservation of life due to reduction in the frequency of fat embolism syndrome, a known cause of premature death in this context [50]. This issue deserves further studies,and highlights the potential importance of osteoporosis management for the overall health of people with DMD.

In summary, the data presented by Dr. Munns provide evidence to support the 2018 Care Considerations (considered a minimum standard of care), which include pubertal induction in boys with DMD at 12–14 years of age and initiation of ideally intravenous, as opposed to oral, bisphosphonate therapy, at the first sign of vertebral fracture or following a single long bone fracture.

### *A walk-through of pediatric radiographic vertebral fracture evaluation*

Dr. Khaldoun Koujok (Ottawa, Canada) reviewed the approach to evaluation of radiographs assessing vertebral fractures in the pediatric population. He noted the importance of careful patient positioning in order to avoid parallax, and acknowledged that other methods for acquiring spine imaging including "vertebral fracture assessment" by DXA, and EOS™,

both of which are extremely low radiation and not influenced by parallax, may be used as a screening tool instead of plain radiographs [51]. However, plain radiographs may be required in equivocal cases in order to achieve better visualization of vertebral endplates. A recent publication by the International Society for Bone Densitometry discusses the use of vertebral fracture assessment in children [52].

Dr. Koujok further noted that vertebral bodies are scored for fractures according to the Genant semi-quantitative method [53, 54] defined as grade 0 (normal), grade 1 (mild fracture), grade 2 (moderate) and grade 3 (severe). The grading corresponds to the reduction in height ratios when the anterior height is compared to the posterior height (defined as a wedge fracture), the middle height to the posterior height (uniconcave or biconcave fracture), and the posterior height is compared to the posterior height of the adjacent vertebral bodies (crush fracture). The specific height ratios that denote the vertebral fracture grades are as follows: Grade 0: $\leq$20%; Grade 1: >20 to 25%; Grade 2: >25 to 40%; Grade 3: >40%. An incident fracture is defined as an increase in the Genant grade by at least 1 compared with a prior image, as previously described [55]. This method has been validated in children with chronic conditions treated with glucocorticoid, by showing that vertebral fractures are associated with biologically-relevant factors including back pain, low and declining DXA LS BMD Z-scores, low second metacarpal percent cortical area Z-scores [11, 27, 56, 57], and an increased likelihood of new vertebral and long bone fractures [11]. Therefore, prompt recognition and clear reporting of vertebral fracture, including, grading of fracture severity, are important for optimal clinical care.

Children demonstrate physiological anterior rounding of the vertebral body in the mid-thoracic region, a phenomenon which is typically represented by about 10 degrees loss in vertebral height ratio. In cases where physiological anterior rounding of the vertebral body in the mid-thoracic region is difficult to distinguish from a vertebral fracture, the decision to adjudicate a vertebral body as fractured can be facilitated by qualitative signs, including endplate interruption, loss of endplate parallelism, and anterior cortical buckling (the latter, a relatively rare manifestation of vertebral fractures in children) [27]. Anterior cortical buckling is an uncommon type of fracture in children because the anterior cortex of the vertebral body is not fully formed until the second decade. Vertebral fractures can mimic normal variants beyond the physiological wedging of young children, as described in an atlas compiled from children with glucocorticoid-treated disorders describing both vertebral fractures, and normal variants [58]. This underscores the importance of expertise in adjudicating vertebral fractures in clinical and research settings.

By showing that vertebral fractures are linked to biologically-relevant factors including back pain, DXA LS BMD Z-scores, and second metacarpal percent cortical area Z-scores [11, 27, 56, 57], the Canadian Steroid-associated Osteoporosis in the Pediatric Population (STOPP) Consortium validated that >20% loss of vertebral height ratio according to the Genant semi-quantitative method [53, 54] is an appropriate definition of vertebral fractures in the young. Validity was also affirmed in a study of children with leukemia, in whom Genant-defined vertebral fractures at diagnosis were the strongest predictor of new vertebral *and* long bone fractures over the next five years [11]. Dr. Koujok noted that people with DMD do not demonstrate the potential for vertebral body reshaping (unlike children with leukemia where the risk factor to the skeleton is transient), due to the persistence of risk factors for ongoing vertebral collapse including the progressive myopathy and ongoing high-dose glucocorticoid therapy.

*Patient stories*

A carer of a young person with DMD and an adult man with DMD shared their experiences of bone-related complications.

Amanda Illes shared the very tragic story of her adolescent son who sadly died within hours of a simple fall without a fracture. The cause of death was fat embolism syndrome which is a rare but known complication following a fracture of the long bone or fall without a fracture in people with DMD. Fat embolism syndrome after a fall or fracture has been previously described in DMD, and discussed in the earlier section in this report by Dr Weber. Education of the patient community on this serious complication is critical. There is a need to consider how this is appropriately and sensitively discussed in the clinic, with families and the young person with DMD.

Justus Kujjer, a 30-year-old man with DMD, shared his experience of painful vertebral fractures which presented clinically in his early 20 s. Justus was managed with 10 days on/10 days off glucocorticoid since early childhood. His experience highlighted a few important points including that vertebral fractures can still be observed in people with DMD on

10 days on/10 days off glucocorticoid, even though less common than those on daily therapy [20], and the impact of painful vertebral fractures on the day to day living and upper-limb function of adults with DMD. Justus believed that the decline of his upper limb function was hastened in part due to the pain from vertebral facture and not being able to use his manual wheel-chair. Justus also shared his more recent experience in his late 20 s where his lateral spine x-ray was said to be normal by doctors in the emergency department despite severe new onset back pain. A computerised tomography scan of the spine, however, identified new vertebral fracture. This highlights the need for clinicians to consider alternative forms of imaging if there is severe back pain if radiographs are non-diagnostic.

## IMPLEMENTING STANDARDS OF CARE: CHALLENGES AND LESSONS LEARNT

### *Word Duchenne Organization and its role in the global implementation of standards of care*

Elizabeth Vroom (Netherlands) presented the active role of World Duchenne Organization in the dissemination, translation, and implementation of 2018 Care Considerations. An international conference on this subject was organized in year 2018 in Amsterdam and the presentations are available online for the global community [59]. International experts discussed the various updates to multidisciplinary care of people with DMD, including bone and endocrine considerations, in the meeting in 2018. A subsequent online international care conference was also held in 2021, and this was followed by an online care conference in 2022 with focus on care of adults with DMD. Endocrine and bone health were discussed in both online care conferences (2021 and 2022), and available on the World Duchenne Organization YouTube channel [60, 61]. The collaboration of four not-for-profit organizations: Muscular Dystrophy Association, Parent Project Muscular Dystrophy, TREAT-NMD and World Duchenne Organization, led to the development of the Duchenne Family Guide which is a patient friendly version of the 2018 Care Considerations for DMD [62]. The family guide is available online in 19 different languages [63]. For children with DMD and their families, short animated videos were developed by World Duchenne Organization to help families better understand optimal care, including bone health, puberty and adrenal insufficiency and other emergencies, which are available online in 9 different languages [64]. World Duchenne Organization takes an active interest in promoting good standards of care for people with DMD world-wide and has always promoted attention to care in the area of bone and endocrine management.

### *The Parent Project Muscular Dystrophy certified centres approach in the United States of America*

Rachel Schrader (USA), Vice President, Clinical Care & Education at Parent Project Muscular Dystrophy (PPMD), presented the Certified Duchenne Care Center (CDCC) program, a unique initiative of PPMD. PPMD is a strong advocate for the provision of Duchenne-specific, comprehensive, standardized care and management to people living with DMD.

Now in its 10th year, the CDCC program, led by PPMD's director of Care and Education and made up of members of the Duchenne community (industry, healthcare providers, and families), aims to standardize and improve care through the evaluation and certification of centres that provide comprehensive clinical care and services to people living with DMD. Centres that meet the CDCC Program criteria may be certified as a CDCC by the Certification Committee comprising American experts in Duchenne care. The CDCC program also includes an advisory committee for the purposes of ongoing programmatic operations and refinement. The certification process involves a voluntary application, completion of both the Clinical and Subspecialty Services Survey and Duchenne Care Survey, a site visit including faculty and staff interviews, as well as a review of patient records. Comprehensive patient information and fact sheets developed by PPMD in all aspects of care including bone, growth, puberty are available online [65]. These are available in English and Spanish. Emergency cards including large weatherproof cards which can be attached to wheelchairs are also available.

PPMD's CDCC network includes 36 centres across the United States and 2 international ones (one in the Czech Republic and one in Johannesburg, South Africa). Together, these CDCCs improve access to comprehensive Duchenne care, participate in PPMD's annual Healthcare Summit and continue to accelerate improvements in care and treatment. As part of the certification process, centres are evaluated for their ability to meet minimum standards as set forth in the 2018 Care Considerations, including in areas of bone and endocrine care [12–14].

*The Duchenne Centre Netherlands approach in the Netherlands*

Dr. Erik Niks (Netherlands) presented the implementation of the 2018 Care Considerations in the Dutch healthcare system, which was done via a nationwide collaboration including two projects. The first was via the Federation of Medical Specialists (FMS) consisting of a GRADE analysis and a formal literature review. Results were published online in March 2021 [66], including ten modules focused on the treatment of patients with DMD, such as optimal treatment with glucocorticoid and prevention and management of scoliosis. The second project involved 12 working groups of health care professionals from all Dutch university medical centres and patient representatives who had several online discussions on remaining topics not covered in the FMS guidelines in order to reach consensus on clinical practice. Results on Endocrinology and Bone health were made available online on the website of the Duchenne Centre Netherlands (DCN) in March 2021 [67]. In addition, the Dutch Dystrophinopathy Database is a hybrid nationwide registry also capturing data from outpatient care in the DCN centres in Leiden and Nijmegen [68]. Such an approach aims to harmonize, improve clinical care in DMD, but also capture data that may allow the development of evidence-based care guidance in the future, and is an important project with the potential for wider collaboration with international colleagues.

*The DMD Care UK approach in the UK NorthStar Network and National Health System*

Cathy Turner (United Kingdom), Project Manager for DMD Care UK, highlighted the role of this project, in regard to implementation of the updated international Care Considerations at a national level. DMD Care UK [69] is a joint initiative between Newcastle University and Duchenne UK, in partnership with NorthStar clinicians [70], which consists of 27 clinical sites delivering care to paediatric patients with DMD in the UK. DMD Care UK aims to harmonise standards of care across the UK for all people living with DMD by reaching consensus through expert working groups and wide consultation across patient and clinical communities, adapting the 2018 Care Considerations into UK-centric recommendations. Existing clinical provision for DMD across the UK was reviewed via a clinician survey (2019) and a patient survey (2020) in all aspects of care. Gaps and barriers to implementation were identified, along with a practical, pro-active approach to overcoming these. This includes raising awareness, education, research to address gaps in evidence and making a business case to providers (the National Health Service). Endorsement of DMD Care UK's output recommendations by national professional bodies is key to the project.

The DMD Care UK Bone and Endocrine Clinical Guidance was released in 2020 and endorsed by the British Society of Paediatric Endocrinology and Diabetes (BSPED). It included practical recommendations on oral steroid sick day dosing plans, which was not included in the 2018 international Care Considerations. The guidance is due to be revised to ensure alignment with UK national guidance for acute management of paediatric adrenal insufficiency developed by BSPED in 2022, which also includes hospital management of adrenal insufficiency during acute emergencies and during the peri-operative period [71]. Other outputs from this workstream in DMD Care UK include patient information leaflets on delayed puberty, adrenal insufficiency and osteoporosis which includes information on plans to mitigate first dose bisphosphonate reactions. A DMD steroid dependent medical alert bracelet, and an in case of emergency DMD smartphone app, are also available for patients without any cost. This project, including the bone and endocrine working group of DMD Care UK has the ambition to drive change in care at a national level; and to collaborate with international experts to share best practice and develop new care pathways, taking into account the changing landscape of DMD and management approaches.

*Moving beyond the 2018 Care Considerations*

*Significant bone loss following cessation of ambulation in DMD*

Dr. Nicola Crabtree (Birmingham, United Kingdom) presented her group's study assessing the profoundly negative impact of loss of ambulation on bone development in boys with DMD, highlighting the importance of skeletal loading, and the precipitous changes that occur once skeletal loading is lost. Fifty boys with DMD were followed over two years using peripheral quantitative computed tomography of the forearm and lower leg (a three-dimensional assessment, one that is not affected by bone size), in addition to muscle function assessments, to document changes in bone and muscle strength. All boys with DMD were or had been taking oral pred-

nisolone using either the 10 days on/ 10 days off regime, the alternate day regime, or the daily regime [72].

At baseline, compared to healthy boys, boys with DMD had significantly reduced trabecular BMD, bone size, cortical thickness and muscle density at the radius, ulna, fibula, and tibia. Boys with DMD who subsequently lost independent ambulation, also had significantly reduced muscle function. After two years, boys with DMD who became non-ambulant lost significantly more bone, most notably at the distal tibia, with 53% less trabecular volumetric BMD than their healthy age-matched peers. The loss of bone was mirrored by losses in both muscle density and function.

The study highlighted that reduced muscle function and lack of loading following loss of ambulation hastens the trajectory of bone loss especially at distal tibia, a weight-bearing site. Using clinically measurable muscle function testing to predict loss of ambulation may help identify the optimum time point at which medical intervention to strengthen or maintain bone strength should be administered; and such studies are now needed.

*The vertebral fracture cascade in DMD*

Dr. Jarod Wong (Glasgow, UK) discussed "the vertebral fracture cascade in DMD", first described in pediatric DMD by Ma et al. in a retrospective study assessing the time to and determinants of first fractures [3]. The extent of osteoporotic vertebral fractures and the vertebral fracture cascade are well described in groups of children treated with long-term GC [57, 73, 74]. The 2018 Care Considerations for DMD recommend routine lateral thoracolumbar spine imaging to identify vertebral fractures and that intravenous bisphosphonates should be initiated even with asymptomatic moderate and severe vertebral fractures [12]. Dr. Wong presented the experience of annual lateral spine monitoring in boys with DMD and management with intravenous bisphosphonates in Glasgow since 2015. In his preliminary report, eleven boys with DMD (all on daily glucocorticoid) had one to two mild (Genant 1) vertebral fractures identified on routine annual spine imaging and who were asymptomatic when fractures were first identified. With follow-up without bisphosphonate therapy, all boys developed either new vertebral fractures (Genant 1 and genant 2) or further collapse of existing fractures (Genant 2 or 3). Ten of the 11 boys reported back-pain with follow-up. These preliminary results provide evidence to consider initiation of bisphosphonates even when mild asymptomatic vertebral fractures are first identified especially in those on the highest-risk regimen (daily glucocorticoid). Given the extent of osteoporotic fractures in boys with DMD on glucocorticoid [1, 75], in particular daily therapy [1, 20], there is now discussion about initiating osteoporosis therapies prior to first fractures, with data collection in different centres to explore whether outcomes can be improved when bone-targeted therapy precedes the onset of the vertebral fracture cascade.

*Clinical predictors of vertebral fractures in DMD*

Dr. Kim Phung (Ottawa, Canada) presented her data assessing risk factors for and predictors of vertebral fractures in DMD [76]. In this group's 12-month prospective bi-centre study of 60 glucocorticoid-treated males with DMD aged 4–25 years, they showed that 19/60 (32%) of patients had at least one prevalent vertebral fracture at baseline (after an average of 4.5 years of GC exposure) [76]. Dr. Phung's work further identified that an increase in the average daily GC dose along with other markers of systemic glucocorticoid exposure, including shorter stature, increased weight, lower DXA LS BMD Z-score, and delayed bone age each were independently associated with an increased odds of one or more prevalent vertebral fractures [76]. The 12-month data from this cohort showed that incident vertebral fractures after an additional 12 months were observed in 24% of patients [77]. Vertebral body reshaping following vertebral fracture was not observed in any participant in the absence of bone-active therapy. The strongest predictor of 12-month incident vertebral fractures in this cohort of glucocorticoid-treated DMD was the presence of clinically significant fragility fractures (prevalent vertebral fracture or historical non-vertebral fracture), along with greater skeletal maturational delay assessed by bone age on hand x-ray.

Dr. Phung's finding that prevalent vertebral and historical non-vertebral fractures were the strongest predictors of new vertebral fractures support an overall shift from timely secondary prevention towards primary prevention of first-ever fractures in DMD. Furthermore, her data showing that clinical markers of glucocorticoid exposure were also associated with fractures will assist in prioritizing which boys

with DMD merit primary prevention efforts more urgently.

*Oral bisphosphonate therapy in DMD*

Dr. Brenda Wong (Worcester, USA) presented her group's data on oral bisphosphonate (alendronate) therapy for mild (Genant 1) vertebral fractures or declining LS and total body BMD without fractures in DMD. With the need for prolonged use of glucocorticoid therapy and the unwanted exacerbation of osteoporosis risk, a proactive approach including optimal calcium and vitamin D intake, and oral alendronate (starting dose 17.5 mg weekly in patients aged 5–7 years, 35 mg once weekly in those aged 8 years and older) was adopted for bone health management of glucocorticoid-treated DMD patients attending the Comprehensive Neuromuscular Clinic at Cincinnati Children's Hospital Medical Center from 2005 to 2017 [37]. Oral alendronate was associated with increases or stabilization of BMD of the LS and region 1 of the lateral distal femur, an effect which was sustained on average up to three of the six years of observation. Beyond three years, there were significant declines in DXA LS, total body, and lateral distal femur BMD Z-scores slopes compared to the initial three years post-alendronate initiation. Oral bisphosphonates were well-tolerated, with no patient reporting any side effects (consistent with low oral bioavailability relative to intravenous therapy).

Twenty-seven patients out of 43 who had serial spine radiographs had at least one vertebral fracture at baseline. During alendronate treatment, pre-existing vertebral fractures remained unchanged in 18 patients (18/27, 67%), worsened in four patients (4/27, 15%) and improved in 5 patients (5/27, 18%). Over six years on alendronate, ten patients (10/43, 23%) developed asymptomatic mild vertebral fractures and five (5/43, 12%) developed symptomatic moderate or severe vertebral fractures (5/43, 12%).

These findings suggest that the proactive use of oral alendronate may play a role in preventing initial, but not sustained, decline in DXA LS aBMD Z-score (and lateral distal femur BMD Z-score adjacent to the growth plate, but not TBLH BMD Z-score), in the first few years of glucocorticoid therapy if moderate and severe osteoporosis are absent. Given evidence that the oral bioavailability of alendronate is less than 1% [40], and that the benefits to LS and lateral distal femur BMD are not sustained beyond three years, clinicians will need to weigh the value of fewer side effects but apparently lower efficacy of oral bisphosphonates against the greater efficacy but correspondingly more first-exposure adverse effects of intravenous bisphosphonate therapy in this setting.

*Patients' voice on moving beyond the 2018 Care Considerations*

Pat Furlong (USA), President and CEO of Parent Project Muscular Dystrophy, shared the patient's perspective on the current 2018 Care Considerations and the path forward for bone health management in DMD. Bone heath is a major concern for individuals with DMD. Given the assessment of BMD and spine imaging for vertebral fractures early in the course of the disease, families become very aware of the risk of fragility fractures. The adverse effects of prolonged GC therapy, which is initiated soon after the diagnosis, further impacts bone fragility. While the 2018 Care Considerations promoted both earlier and more comprehensive osteoporosis monitoring in order to identify and treat bone strength loss in a timelier fashion with bisphosphonate therapy than in the past, this approach still falls significantly short of the mark for families. This is because of the devastating effects of first long bone fractures in DMD including permanent, premature loss of ambulation and death due to fat embolism syndrome, and an overall increased risk of subsequent fractures combined with lack of potential for spontaneous osteoporosis resolution given the progressive myopathy. Changes in vertebrae can be seen on spine radiographs soon after initiation of GC, with a high proportion of patients experiencing vertebral fractures and long-bone fractures with follow-up.

Despite recommendations of the 2018 Care Considerations, some physicians recommend oral bisphosphonates upon initiation or within the first year of glucocorticoid therapy. Other centres wait until the first fracture occurrence before initiating intravenous bisphosphonates. Patients and families are hopeful for a forward-moving approach that introduces an effective bone-sparing regimen to prevent first fractures in DMD. It is recognized, however, that until such a time as there is an available agent that more completely rescues dystrophin, or a bone-targeted therapy that over-rides the adverse effect of the myopathy on bone strength by increasing not only BMD but bone size, efforts to prevent all low-trauma fractures are likely to continue to be lacking.

## EMERGING NEW UNDERSTANDING AND THERAPIES FOR MUSCLE-BONE OUTCOMES IN DMD

*Summary of DMD related abstracts from the International Conference on Children's Bone Health*

Dr. Frank Rauch (Montreal, Canada) summarized the DMD-related abstracts from the 10th International Conference on Children's Bone Health (ICCBH), the largest international scientific gathering on childhood-onset bone disorders, which was held in Dublin, Ireland, from July 2 to 5, 2022. The meeting showcased that DMD-associated bone disease is high on the agenda of pediatric bone specialists. Among the 23 top-ranking abstracts that were selected for oral presentation, four focused on bone issues associated with DMD. In addition, 12 of the 173 poster presentations dealt with DMD-associated bone disease. Thus, the conference highlighted the fact that bone health in DMD currently is an important area of concern.

*RANKL inhibition and musculoskeletal outcomes in an animal model of DMD*

The binding of receptor activator of nuclear factor kappa beta ligand (RANKL) to its receptor RANK triggers osteoclast precursors to differentiate into bone resorbing osteoclasts. RANKL and RANK are expressed in bone and skeletal muscles [78] so targeting RANKL may have advantages in DMD by ameliorating dystrophic skeletal muscle function in addition to their anti-resorptive properties, as previously shown by Hamoudi et al. [79]. In addition, anti-RANKL antibody may also be more convenient to administer in the clinic due to the sub-cutaneous route of administration of the medicinal form of this agent, denosumab.

Dr. Soher Jayash (Edinburgh, United Kingdom) presented experimental results investigating the potential for anti-RANKL treatment to prevent glucocorticoid-induced bone loss and promote muscle function in dystrophic mice [80]. Dystrophin-deficient *mdx* mice were treated with IgG (control), deflazacort [2 mg/kg/day], anti-mouse RANKL [4 mg/kg/3d] or both deflazacort and anti-RANKL for eight weeks. Anti-RANKL and deflazacort each improved grip force of *mdx* mice independently, but a synergistic effect of the combined treatments was not noted. However, anti-RANKL, but not deflazacort, improved *ex vivo* contractile properties of dystrophic muscles ($p < 0.01$). The data also showed that mdx mice treated with both deflazacort and anti-RANKL led to improved bone microarchitecture, as evidenced by significantly higher trabecular bone volume/total volume ($p < 0.05$) and lower trabecular separation ($p < 0.001$) of the vertebra (L6) compared to mdx mice treated with deflazacort only. These pre-clinical results provide support for the consideration of targeting RANKL as osteoporosis therapy in DMD and the development of clinical trials to explore its role for improvement in skeletal muscle outcomes in comparison with glucocorticoid.

*The role of denosumab for osteoporosis management in DMD*

Dr. Ward reviewed the rationale and preliminary results of a randomized, open-label, single-blind (x-ray central readers), pilot controlled trial of zoledronic acid versus sub-cutaneous denosumab in boys with DMD (NCT 02632916). Dr. Ward's rationale for such a study was that the first-infusion side effects of intravenous bisphosphonate therapy, along with the inconvenience of the intravenous route, have spurred interest in alternative forms of anti-resorptive therapy for children with osteoporotic conditions, including DMD. While oral bisphosphonates are a possibility, their demonstrated low bioavailability in children with osteogenesis imperfecta and glucocorticoid-treated disorders (less than 1% with oral alendronate) [39, 40] and failure to achieve anti-fracture and functional goals in large, randomized trials of children with osteogenesis imperfecta [41, 81] have led to consideration of more potent anti-resorptive agents, including denosumab. Large studies in adults have shown that denosumab 60 mg every six months reduces hip, vertebral, and non-vertebral fracture risk without an increased frequency of adverse events compared with placebo [82]. Other adult studies have also confirmed that adverse events with denosumab are similar to an active comparator (oral alendronate), including the frequency and magnitude of hypocalcemia [82, 83]. Denosumab is approved for osteoporotic men and post-menopausal women with a high risk of fracture and for adult glucocorticoid-induced osteoporosis.

The compassionate use of denosumab has been reported in a few bone disorders of childhood such as osteogenesis imperfecta [84], giant cell tumours [85], aneurysmal bone cysts [86], and fibrous dysplasia [87]. However, its use has been challenging in chil-

dren with normal or high bone turnover due to "the rebound phenomenon". The "rebound" (or "overshoot) phenomenon is characterized by a decline in BMD and an increase in vertebral fractures following denosumab discontinuation in adults [88], and the potential for these complications along with frank hypercalcemia-hypercalciuria in children [89]. The rebound phenomenon appears to arise from exuberant skeletal resorption following reactivation of osteoclasts when the effect of the antibody wanes.

Dr. Ward reviewed that in glucocorticoid-treated DMD, where bone turnover is invariably low, and often profoundly so, she hypothesized that the rebound phenomenon may not be a concern unless bone turnover is normal or otherwise activated post-baseline (such as in patients receiving newer treatments like vamorolone, or in boys going through spontaneous or induced puberty) [90]. The fact that RANKL is also implicated in the DMD muscle inflammatory pathway [91], and that anti-RANKL antibody given to the mdx mouse decreases muscle inflammation, creatine kinase levels and improves the digitorum longus muscle specific force [79], provided further rationale for the use of denosumab in the DMD setting.

Dr. Ward reviewed her pilot data in eight boys with genetically-confirmed DMD and a history of at least one osteoporotic vertebral or long bone fracture, all treated with daily GC therapy. Boys were randomized to intravenous zoledronic acid 0.025 mg/kg every six months or sub-cutaneous denosumab 1 mg/kg every six months, both for two years. The mean age at enrolment was $9.8 \pm 1.9$ years and $10.1 \pm 1.3$ years on denosumab. Preliminary, unpublished safety and efficacy results over the two years of the study were presented descriptively given the pilot nature of the work and small sample size. In both groups, boys were considerably shorter and heavier than the healthy average, and BMD trajectories were favourable (LS and hip areal BMD by DXA, and distal tibia trabecular volumetric BMD). In addition, back pain declined in all patients in both groups, as did the Spinal Deformity Index (sum of the Genant grades). There were no serious adverse events; however, the four boys on zoledronic acid had a total of 17 drug-related adverse events (most within 10 days of the first infusion), whereas only one drug-related adverse event was reported on denosumab (a mild injection site reaction). Furthermore, serum bone turnover markers remained suppressed relative to baseline in both groups over the two years of the study, and there were no episodes of hypercalcemia or evidence of nephrocalcinosis on denosumab after two years. At the time of this Symposium's live presentation in November 2022, all boys had continued denosumab following the two-year trial.

However, 10 months post-symposium, Dr. Ward observed that one of the boys originally enrolled in the study presented with asymptomatic hypercalcemia, along with a precipitous rise in serum CTX-a marker of bone resorption, six years after denosumab initiation and just prior to his next denosumab dose. There were no other causes for the hypercalcemia identified; therefore, Dr. Ward concluded that this boy did indeed manifest the denosumab-induced hypercalcemic rebound phenomenon. The hypercalcemia resolved quickly following a small, single dose of pamidronate 0.25 mg/kg, and the patient has now been transitioned to bisphosphonate therapy for the prevention and treatment of osteoporosis. Interestingly, this teenage boy had recently started testosterone therapy for pubertal induction. Whether the anabolic effect of testosterone contributed to the denosumab-related rebound phenomenon remains unknown. Given this observation, Dr. Ward has cautioned against using denosumab monotherapy for the treatment of DMD-related bone fragility (*personal communication*). This is unfortunate, since the tolerability of denosumab, apart from the hypercalcemia, was favourable for denosumab and an improvement in this pilot study over the first-exposure side effects observed with intravenous zoledronic acid. There may nevertheless be clinical scenarios in DMD where the benefits of denosumab outweigh the risks. For this reason, it is recommended that if denosumab is to be used, it is administered by clinicians working in specialized centres who hold the necessary expertise and monitoring tools to ensure the child's safety.

### *Vamorolone: Impact on skeletal muscle and bone outcome*

Efforts are underway to treat the aggressive myopathy of DMD with agents that are less toxic to bone and other organ systems than classic glucocorticoids (i.e. prednisolone and deflazacort in the setting of DMD). Drs. Eric Hoffman (Binghamton, USA) and Stefan Jackowski (Ottawa, Canada) presented the latest data on vamorolone in DMD, Vamorolone is an anti-inflammatory dissociative steroidal drug that is chemically distinct from glucocorticoids by lacking a single hydroxyl/carbonyl group at the 11β position of the steroid C ring. The loss of the

hydroxyl/carbonyl group removes one of the contact points with the targeted glucocorticoid receptor, with the ligand/receptor complexes retaining anti-inflammatory properties, but with reduced positive transcriptional activity [92]. This lack of the 11β group also prevents drug/pro-drug conversion by the modulatory 11β-dehydroxy steroid dehydrogenases (HSD11B1, HSD11B2), that have been shown to be required for mediating adverse effects of glucocorticoid at sites of bone formation [93, 94]. Vamorolone, in contrast to glucocorticoids, is also a potent inhibitor of the mineralocorticoid receptor, similar to eplerenone and spironolactone [95].

Dr. Hoffman discussed the muscle outcomes of boys with DMD treated with vamorolone. In a recent phase 2b, randomized, double-blind, placebo- and daily prednisone-controlled 24-week clinical trial (clinicaltrials.gov NCT03439670), daily vamorolone (6 mg/kg/day) displayed superior efficacy in motor outcomes compared to placebo for all five motor outcomes tested (time to stand velocity, 6 minute walk time velocity, time to run/walk 10 meters velocity, time to climb four stairs velocity and North Star Ambulatory Assessment Score [90]. Vamorolone (6 mg/kg/day) also demonstrated similar relative efficacy to daily prednisone in this same trial.

Dr. Jackowski discussed the results of skeletal health evaluations in young, ambulatory boys with DMD who participated in the vamorolone (VBP15) 003LTE longitudinal observational study (clinicaltrials.gov NCT03038399). Vamorolone-treated boys showed improved growth compared with a daily glucocorticoid-treated natural history cohort over 30 months of observation, with increases in weight that were comparable to the natural history cohort [96]. Vamorolone-treated trial participants showed no changes of serum bone turnover marker suppression, compared to prednisone [97]. In a preliminary analysis, the prevalence of vertebral fractures on vamorolone after 30 months of drug exposure was benchmarked to an external comparator study, FOR-DMD. Although the data arose from two different studies, the central imaging radiologists were the same for both studies, and read the lateral spine radiographs according to the same method (Genant semi-quantitative) over similar time periods (from May 2019 to March 2022). This analysis showed that the prevalence of vertebral fractures after 30 months of vamorolone exposure was reduced by more than 50% compared with daily deflazacort and daily prednisone, and that the Spinal Deformity Index (SDI, the sum of the Genant grades) on vamorolone was about 1/3 that of daily deflazacort (where the SDI was the highest), and more than half that of daily prednisone.

Overall, vamorolone is a novel and distinct dissociative steroidal anti-inflammatory, with demonstrated efficacy parity at 6 mg/kg/day to that of daily prednisone (0.75 mg/kg/day), with preservation of linear growth. Preliminary analyses suggest that vamorolone may carry a reduced risk of vertebral fractures compared with daily glucocorticoid therapy. Vamorolone is under regulatory review for drug approval for DMD in the UK, EU, and USA.

## RECOMMENDATIONS AND FUTURE PLANS

This meeting highlighted the high bone morbidity in glucocorticoid-treated DMD, the current minimum international 2018 Care Considerations, and the need to understand how new treatments targeting the underlying myopathy will impact bone health in this condition. Until additional studies evaluating the impact of the changing therapeutic landscape on the skeletal phenotype in DMD are conducted, clinicians should continue to follow, as a minimum, the internationally-endorsed 2018 Care Considerations for osteoporosis monitoring, diagnosis, and treatment. Challenges in implementation of the 2018 Care Considerations were identified, including financial support for bone protection therapy, lack of resources for systematic reporting of vertebral fractures according to the (validated) Genant semi-quantitative method, and lack of DXA machines in some countries to identify declines in LS BMD Z-scores that may prompt spine imaging more frequently than the recommended one to two years on glucocorticoid, or two to three years in those not on glucocorticoid. Table 1 summarizes key aspects to consider in relation to appropriate DXA BMD and vertebral fracture assessment acquisition and reporting which incorporates the recommendations of the 2019 International Society for Clinical Densitometry [97].

At the same time, the threshold for initiation of osteoporosis treatment in DMD should be reconsidered in light of data that re-affirm the high fracture burden, the evidence for the "vertebral fracture cascade" in bisphosphonate-naïve patients with DMD, and the recently-conducted, randomized, controlled trials that have demonstrated the efficacy of bisphosphonate therapy in improving LS BMD in these patients. Considerations for lower thresholds to

Table 1
Key aspects on DXA assessment and vertebral fracture assessment for monitoring and management of osteoporosis in DMD

| Investigations | Recommendations |
|---|---|
| Dual energy absorptiometry (DXA) | We recommend monitoring and follow-up at several skeletal sites; for example, lumbar spine and total body less head [97].<br>Monitoring of femur (proximal or lateral distal femur) is also possible if reference data are available [51, 97].<br>For patients with vertebral fracture(s) at L1-L4, bone mineral density could be assessed by excluding the lumbar vertebra with vertebral fracture [97].<br>Height adjustment is recommended for interpretation of bone mineral density or bone mineral content Z-scores, given that short stature is common in young people with DMD; volumetric adjustment with bone mineral apparent density of the lumbar spine is also appropriate [97].<br>Bone age adjustment is an alternative, especially in older boys who are non-ambulant where height measurement is challenging [98].<br>DXA monitoring is critical in boys with DMD who are receiving bisphosphonates therapy [12]. |
| Vertebral fracture assessment | Vertebral fracture assessment can be performed by lateral spine radiographs or lateral spine image on DXA (the latter also known as DXA vertebral fracture assessment [VFA]) [51, 97].<br>The spine image should include T4 to L5.<br>Vertebral fracture and grading (mild, moderate, severe) should be performed using the Genant semi-quantitative method (L4 to T4), which has been validated in the paediatric population and which defines a vertebral fracture as more than 20% loss in vertebral height ratio.<br>Note that in this high-risk setting, vertebral height loss of 15 to 20% may also be clinically significant, if it represents a visually evident decline over prior observations in a given patient with DMD, especially if there are other radiological features of vertebral fracture like end plate abnormalities [99].<br>Vertebral fracture at L5 should be evaluated by change in shape with follow-up imaging due to the trapezoidal shape of L5 and noted as vertebral fracture or no vertebral fracture.<br>Reporting of vertebral fracture should clearly use the terminology of "fracture" instead of vague terms like "wedging", "reduction in height".<br>Radiological diagnosis of non-fracture vertebral deformities should be included in the report (e.g. normal variants such as physiological wedging in the thoracic region, Cupid's bow, Schmorl's nodes) [58] |



trigger bisphosphonate initiation, including asymptomatic mild (i.e. grade 1,>20 to 25% vertebral height ratio loss) or even longitudinal evidence of vertebral height ratio loss that is < 20%, are currently under discussion, as is initiation of bone protection therapy prior to first non-vertebral fractures (long bone or otherwise). Recent publications which have identified the profile of patients at greatest risk for fractures (including those with clinical signs of systemic glucocorticoid exposure such as short stature, weight increases and bone age delays) [76] and those with declining BMD values due to impending loss of ambulation [72] provide important information that can assist clinicians in prioritizing patients at most urgent need for protection therapy prior to first-ever fractures.

The optimal choice of osteoporosis agent in the sub-clinical (pre-fracture) phase remains a considerable source of debate, given that intravenous bisphosphonates, while more potent and thereby notionally more attractive in the setting of an aggressive osteoporosis such as DMD, carry significant potential for first (and subsequent) infusion side effects. Oral agents, on the other hand, are fundamentally less potent (which has been shown to translate into reduced efficacy for a variety of outcomes in both primary [41, 42] and secondary [43] settings), but may nevertheless play a role in short-term attenuation of LS and lateral distal femur BMD declines in the DMD setting (first three years). In addition, the low bioavailability of oral bisphosphonate therapy also translates into fewer side effects. Denosumab is of interest given studies showing benefit at high doses to muscle strength in murine models of DMD. Preliminary randomized, controlled data of denosumab in a small number of boys with DMD presented in this symposium are encouraging given the positive direction of effect where skeletal health outcomes are concerned, absence of the denosumab "rebound or overshoot" phenomenon, and fewer side effects than intravenous bisphosphonates (zoledronic acid). However, larger, longer-term studies are needed to fully understand the impact of this therapy on the patient's bone health trajectory.

It is recognized that the intensity of osteoporosis monitoring, treatment and prevention paradigms will necessarily vary depending on the strategy employed to treat the underlying condition. At the time of

writing, bone health surveillance and bone protection therapy are needed due to the bone morbidities associated with long term glucocorticoid exposure. Indeed, it is understood that co-administration of glucocorticoid with the potential for future dystrophin restoration therapies like exon skipping and gene therapy will be needed. Ongoing research is needed to understand the relative benefits and risks to endo-bone health arising from different emerging therapies. Until more data are available about the impact of therapies which target the underlying disease, it is recommended that the current standards of care for osteoporosis monitoring and management be maintained on novel DMD-targeted therapy, as a minimum.

Conducting clinical trials to evaluate osteoporosis therapies in pediatric DMD poses significant challenges due to the understandable prioritization of trials targeting the dystrophinopathy since patients cannot participate in more than one experimental therapy at a time. Given the existing obstacles in conducting osteoporosis drug trials for DMD, the implementation of pragmatic real-world studies becomes crucial. These studies should involve standardized clinical treatment protocols and outcomes, including detailed assessment of vertebral fractures and protocolized collection of bone mineral density data, all under stringent quality control measures. The main aim is to evaluate both future primary prevention efforts (introduction of osteoporosis therapies prior to fracture) and ongoing early secondary prevention strategies (introduction of osteoporosis therapies once mild VF is identified) as objectively as possible. Real-world studies of this nature will provide the necessary evidence-based insights to guide the development of updated standards of care for management of osteoporosis in DMD, which will adopt a proactive approach to minimize the risk of initial fractures in this high-risk context.

## CONFLICTS OF INTEREST

AMC serves on advisory boards for Sarepta, Roche, Dyne, and Edgewise. DRW has served as a consultant for PTC Therapeutics. EPH is CEO, co-founder, stock-holder, and sponsor for ReveraGen Biopharma, and CEO, co-founder, stockholder for AGADA BioSciences and is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review. CM has a been a consultant to Kyowa Kirin, BioMarin, Alexion; received research grants from Kyowa Kirin; received speaker's honoraria from Kyowa Kirin; and served on advisory boards for Kyowa Kirin and BioMarin. FR serves on advisory boards for Ultragenyx, Sanofi, and Ibsen. DRW has served as a consultant for PTC Therapeutics; has received grant funding from Inozyme. MG has research collaboration with NIH, PTC Therapeutics, Sarepta, ReveraGen, Pfizer, Roche, Italfarmaco, Santhera, Dynacure, Dyne, and Edgewise; has been on advisory boards for Pfizer, Dyne, NS Pharma; has received speaker's honoraria from Sarepta, Novartis, Roche and Italfarmaco; has received grant funding from Sarepta and PTC Pharmaceutics (through Newcastle University). LMW has received study grants to institution from Ascendis, Catabasis, Edgewise, ReveraGen, Ultragenyx and Amgen, and consultancy fees to institution from Ipsen, Santhera, Amgen, PTC, Alexion and Ultragenyx. SCW has received fundings from Novornordisk (United Kingdom and Australia) for clinical fellowship; has received consultancy fees to institution from Novartis and Santhera; and conference presentation fees to institution from Nutricia. The following authors reported nothing to disclose: KP, NC, PF, SAJ, SJ, AJ, KK, EN, BW, RS, EV.



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