**Statement and Question Codes for "Guidelines for Management of Bone Health in Rett Syndrome Based on Expert Consensus and Available Evidence"**

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| **ROUND 1** |
| **Statement/Question Code** | **Statements and Questions Round 1, Part A, Section 1 (PAS1)** |
| PAS1\_Gene | All children with a clinical diagnosis of Rett syndrome should undergo genetic testing as genotype may influence the development and management of osteoporosis. |
| PAS1\_Fracture | Fractures in Rett syndrome can occur due to trivial trauma. |
| PAS1\_vigilant | Clinicians need to be vigilant for potential fractures. |
| PAS1\_BMI | Measure weight and height to calculate Body mass Index at each clinical visit. |
| PAS1\_Medication | Identify all prescribed medications at each clinical visit, particularly those that can influence bone density: eg anti-epileptic medications, proton pump inhibitors, progesterone-only medications, vitamin supplements. |
| PAS1\_Tanner | Assess pubertal development using Tanner staging. |
| 1. PAS1\_WalkAssist2. PAS1\_WalkTime3. PAS1\_Stand4. PAS1\_StandTime | Assess mobility level by asking about the following:1. The level of assistance needed for walking.2. The time spent walking each day.3. The distance walked each day.4. The amount of time standing in a standing frame if independent standing is not possible. |
| 1. PAS1-24Recall2. PAS1\_FoodVitD3. PAS1\_FoodCalcium | Assess dietary intake including:1. 24 hour diet recall2. Recall of food high in vitamin D.3. Recall of food high in calcium. |
| 1. PAS1\_SunProtect2. PAS1\_Sunlight3. PAS1\_SunTime | Assessment of sunlight exposure by asking about:1. Frequency of use of sunscreen and sun-protection factor/protective clothing.2. The time of the day when skin (equivalent to face and arms) is exposed to direct sunlight.3. Amount of time each day that skin (equivalent to face and arms) is exposed to direct sunlight |
| 1. PAS1\_BiochemCa2. PAS1\_BiochemVitD3. PAS1\_BiochemMg4. PAS1\_BiochemPhos5. PAS1\_BiochemAlk6. PAS1\_BiochemPara7. PAS1\_BiochemAlb | First line biochemical investigations include measurement of:1. Calcium (ideally also ionised calcium).2. 25 hydroxyvitamin D3. Magnesium.4. Phosporus.5. Alkaline Phosphatase.6. Parathyroid hormone.7. Albumin. |
| 1. PAS1\_BiochemElectro2. PAS1\_BiochemUrine3. PAS1\_BiochemMarkers | Second line biochemical investigations include measurement of:1. Electrolytes (ideally also ionised calcium).2. Urine calcium/creatinine ratio (ideally also ionised calcium).3. Bone turnover markers: N-telopeptide, collagen cross-links. |
| PAS1\_Other | Are there any other biochemical investigations that you recommend? |
| **Statement/Question Code** | **Statements and Questions Round 1, Part A, Section 2 (PAS2)** |
| 1. PAS2\_Anticonv2. PAS2\_WalkIndep3. PAS2\_Mutation4. PAS2\_Progest | Bone density should be measured in patients who have no history of fracture but have one or more of the following risk factors:1. Prescribed anticonvulsant medication(s).2. Unable to walk independently.3. Either the p.R168X, p.R255X, p.R270X or p.T158M mutation.4. Oral or intramuscular progesterone only medication. |
| PAS2\_BMDTime | If you agree with measuring bone density in patients with risk factors and no history of fracture, after what duration of presence of the risk factor (excluding mutation type), should bone densitymeasurements commence? For example measure bone density 3 years after taking anticonvulsant medication. |
| PAS2\_LowZScore | If bone density reported Z scores are -2.0 or worse in those patients with risk factors and no history of fracture, should bone density be reassessed and if so within what timeframe? |
| PAS2\_HighZScore | If bone density reported Z scores are better than -2.0 in those patients with risk factors and no history of fracture, should bone density be reassessed and if so within what timeframe? |
| PAS2\_Fracture | Bone density should be measured in patients with a current fracture or a history of fracture (after any methods of external fixation have been removed). For example plastercasting. |
| PAS2\_AltBone | If a long bone was fractured, the bone density should also be measured in the alternate long bone. |
| PAS2\_Vertebrae | If a vertebra was fractured, the bone density may be measured in adjacent vertebrae excluding measurement of the fractured vertebrae. |
| PAS2\_FracLowZScore | If bone density reported Z scores are better than -2.0 in patients with a current fracture or a history of fracture, should bone density be reassessed and if so within what timeframe? |
| PAS2\_FracHighZScore | If bone density reported Z scores are -2.0 or worse patients with a current fracture or a history of fracture, should bone density be reassessed and if so within what timeframe? |
| PAS2\_NoRisk | Should bone density be assessed in patients with no risk factors or history of fracture? |
| PAS2\_NoRiskAge | If you agree that bone density should be assessed in patients with no risk factors or history of fracture, at what age should assessment first commence? |
| PAS2\_NoRiskHighZ | If bone density reported Z scores are better than -2.0 in patients with no risk factors or history of fracture, should it be reassessed and if so within what timeframe, given that no risk factors for osteoporosis develop in the interim? |
| PAS2\_AnnualCheck | Clinically assess patients with no risk factors or history of fracture to check the development of risk factors annually. |
| PAS2\_AnnualCheckLowZ | If bone density reported Z scores are -2.0 or worse in patients with no risk factors or history of fracture, should it be reassessed and if so within what timeframe, given that no risk factors for osteoporosis develop in the interim? |
| **Statement/Question Code** | **Statements and Questions Round 1, Part A, Section 3 (PAS3)** |
| PAS3\_NormData | Where local normative data exists, measure the bone mineral composition and areal bone mass density in the total body minus the cranial bones (headless), and the postero-anterior lumbar spine. |
| PAS3\_Femur | Total hip and proximal femur bone mineral composition and areal bone mass density measurements are not considered a reliable site for measurement due to difficulties with subject positioning |
| 1. PAS3\_Age2. PAS3\_Ht3. PAS3\_Wt | Z scores should be calculated from raw values for the following:1. Age.2. Height.3. Weight. |
| PAS3\_BMAD | Bone mineral apparent density (or volumetric bone mass density) adjustment is also recommended where possible. |
| PAS3\_SameSite | The same skeletal sites should be assessed when repeating densitometry measures longitudinally. |
| PAS3\_Rods | In individuals with spinal rods, the bone mineral composition and areal bone mass density for the femoral neck and the total body minus the cranial bones (headless) should be measured. |
| PAS3\_ReduceMove | What strategies would you use to reduce unnecessary movement during the densitometry scan procedure? |
| PAS3\_LTM | Where possible densitometry measurements of lean tissue mass should be assessed. |
| **Statement/Question Code** | **Statements and Questions Round 1, Part B, Section 1 (PBS1)** |
| PBS1\_PA | Increase physical activity in order to increase muscles strength and bone density |
| PBS1\_Physio | In order to increase physical activity refer to a physiotherapist for development of an optimal physical activity plan. |
| 1. PBS1\_Standing2. PBS1\_Frame | For those who are wheelchair bound, where possible:1. Encourage supported standing during transferring.2. Use a standing frame for at least 30 minutes a day |
| PBS1\_WalkTime | For those who are able to walk, aim to increase the distance and/or the length of time walked each day (at least 2 hrs per day where possible). Please comment on recommendations you have regarding timeframe. |
| 1. PBS1\_Treadmill2. PBS1\_Vibration | Where mobility is limited use of the following is recommended:1. Body weight supported treadmill.2. Whole body vibration therapy. |
| PBS1\_Calcium | If calcium intake is low, increase dietary intake of calcium rich or calcium fortified foods. |
| PBS1\_CaSupp | If dietary calcium intake is low and difficult to increase using dietary means, prescribe calcium supplements to meet the local recommended daily intake. The current recommended dietaryintake levels within Australia are: 1-3yr 500mg/day, 4-8yr 700mg/day, 9-11yr 1000mg/day,12-13yr 1300mg/day, 14-18yr 1300mg/day, >18yr 1000mg/day. |
| 1. PBS1\_VitDProtocol2. PBS1\_VitDReassess | If 25 hydroxyvitamin D levels are lower than 75nmol/litre (mg/dl):1. Use local protocols for treatment and supplementation.2. Re-assess 25 hydroxyvitamin D levels after 4-8 weeks, then annually. |
| PBS1\_Sunlight | Advise an appropriate amount of sunlight exposure based on latitude, time of day, season and skin type. |
| **Statement/Question Code** | **Statements and Questions Round 1, Part B, Section 2 (PBS2)** |
| PBS2\_Bisphos | Bisphosphonates should be used if the International Society for Clinical Densitometry criteria for osteoporosis in children and adolescents are fulfilled. |
| PBS2\_IVBisphos | The intravenous dosage of bisphosphonates should follow local protocols. |
| PBS2\_ReassessBMD | Reassess bone mineral composition and areal bone mass density one year after Bisphosphonate therapy. |
| PBS2\_ReviewTreat | If reassessment of bone mineral composition and areal bone mass density shows limited response, review the therapeutic approach. |
| PBS2\_Prog | Levonorgestral implants or combined oral contraceptives are associated with less adverse impact on bone density compared to progesterone only medication. |
| PBS2\_LowContra | Low dose oral contraceptives (30-40 micrograms ethinyl estradiol) are protective of bone density. |
| PBS2\_UltraLowContra | Ultra-low dose oral contraceptives (20 micrograms ethinyl estradiol) may negatively impact bone density if started soon after puberty. |
| PBS2\_Mirena | Although Levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena) does not negatively affect bone density, communication difficulties during insertion need to be considered. |
| PBS2\_DMPA | Avoid use of Depot medroxyprogesterone acetate (DMPA) as this may increase risk of fracture. |
| **ROUND 2** |
| **Statement/Question Code** | **Statements and Questions Round 2, Part A, Section 2 (PAS2)** |
| 1. PAS2\_Anticonv2. PAS2\_Mutation3. PAS2\_Progest 4. PAS2\_WalkIndep | Bone health needs to be considered early on in life and routine risk factors assessed, such as:1. Prescribed anticonvulsant medication(s).2. Either the p.R168X, p.R255X, p.R270X or p.T158M mutation.3. Oral or intramuscular progesterone only medication.4. Unable to walk independently. |
| PAS2\_Baseline | In the presence of risk factors, bone density baseline measurements should be performed. |
| 1. PAS2\_DXA2. PAS2\_LateralSpine3. PAS2\_PQCT | Consider using the following techniques to assess bone health:1. Densitometry 2. Peripheral quantitative computed tomography 3. Lateral spine X-ray |
| PAS2\_MonitorBD | Monitor bone density every 1-2 years depending on clinical features. |
| **Statement/Question Code** | **Statements and Questions Round 2, Part A, Section 3 (PAS3)** |
| 1. PAS3\_Age2. PAS3\_Ht | Z scores should be calculated from raw values for the following:1. Age.2. Height. |
| PAS3\_ReduceMove | To reduce unnecessary movement during bone density scan procedures, calming techniques such as music and the presence of careers/parents or sedation may be used. |
| **Statement/Question Code** | **Statements and Questions Round 2, Part B, Section 1 (PBS1)** |
| PBS1\_TargetExercise | Where mobility is limited, targeted exercise such as body weight supported treadmill or assisted walking are recommended. |
| **Statement/Question Code** | **Statements and Questions Round 2, Part B, Section 2 (PBS2)** |
| PBS2\_DMPA | If hormonal intervention for regulation of the menstrual cycle is needed, use of Depot medroxyprogesterone acetate (DMPA) should be avoided. |