D.22 Monitoring for low BMD

Item	Details
Issue in the scope	Surveillance for reduced bone mineral density.
Review question in the scope	How should monitoring be carried out to identify reduced bone mineral density?
Review question for the protocol	What is the most effective strategy to monitor for the identification of reduced bone mineral density in people with CF?
Objective	The increase in life expectancy of cystic fibrosis (CF) patients has brought about a rise in new clinical problems in these patients, such as a decrease in bone mineral density (BMD). The cause of diminished BMD in CF is multi-factorial and can lead to osteoporosis. It is of clinical importance to identify bone disease related to CF early in its course to allow therapeutic interventions that optimize bone health. BMD is usually normal in well-nourished children with CF who have good lung function. Even so many patients fail to gain bone normally, or experience premature bone loss, in adolescence. About one third of adults with CF have low bone mineral density, which may predispose them to bone fractures. CF-related low BMD probably has many causes: 1. Bone health is strongly linked to the severity of lung disease and body weight. Severely ill patients are more likely to have low BMD. Conversely patients with normal weight and height, and good lung function, have near normal bone density. Lung infection in CF is associated with more intense inflammation and raised levels of chemicals called cytokines in blood and sputum. These cytokines increase the activity of cells which break down bone. 2. Apart from the general malnutrition associated with more severe disease, many aspects of nutrition affect bone status, including vitamins (e.g., vitamins D and K), minerals (e.g., calcium), and protein intake. 3. Oral corticosteroids cause rapid bone loss, especially during the first year of therapy. They reduce calcium absorption from the gut, increase calcium loss in the urine, decrease the number of bone-forming cells and increase bone resorption. Most of the larger studies in individuals with CF have shown an association between oral steroid use and low BMD. 4. A number of studies in people who do not have CF have found an association between greater physical activity and higher BMD levels. However, it is not known if weight-bearing exercise in people with CF can increase peak bone mass, preserve BMD or increase BMD in those with low BMD. 5. Despite most children with CF achieving normal or near normal growth, puberty is often delayed. Bone mineral deficiencies resulting from late onset of puberty may not be corrected when puberty eventually starts. Low sex hormone levels, oestrogen and testosterone, are associated with low BMD in adults with cystic fibrosis. 6. Low bone mineral density has been associated with CF-related diabetes. 7. There may be a direct link between CF-related low BMD and the abnormal protein produced by the CF gene. Lung infection damages bone health. Therefore treatments that prevent the progression of lung disease should be optimised.
Language	English
Study design	• Systematic reviews • RCTs (test and treat) • Conference abstracts of RCTs (Only if RCTs unavailable and the quality assessment of abstracts will conducted based on the available information and if necessary the authors of abstracts will be contacted). • Prospective or retrospective cohort studies (only if RCTs unavailable or limited data to inform decision making)

© NICE 2017. All rights reserved. Subject to Notice of rights.

Item	Details
Population and directness	Infants, children, young people and adults with defined CF, diagnosed clinically and by sweat test or genetic testing. Population size and indirectness: • No sample size specification. • Studies with indirect populations will not be included
Stratified, subgroup and adjusted analyses	Groups that will be reviewed and analysed separately: • Gender (male versus female) • Age (≤10 years versus 11 to 17 years versus ≥18 years) • Puberty staging • Patients with osteoporosis and osteopenia Sensitivity analysis: In the presence of heterogeneity, sensitivity analysis will conducted including and excluding studies with a high risk of bias.
Prognostic test	• Regular DXA scans • Peripheral quantitative computed tomography (pQCT) Notes: • Challenges for interpretation of bone densitometry data: good reproducibility is dependent on the quality of the scanning procedure, which itself is dependent on the correct positioning of the patient, the protocol used for analysis and the systematic use of a calibration phantom. Precision can be further enhanced for longitudinal BMD measurements through using the same densitometer/ analysis software and the same operator as for the original measurement. • BMD measured by dual energy X-ray absorptiometry (DXA) – gold standard. • DXA scans should be performed in centres experienced in interpreting BMD data from people with CF. • Normative data should be age, gender and geographically matched to the patients measured. • BMD should be measured at the total body and the lumbar spine in patients younger than 20 years of age, and at the lumbar spine and proximal hip in patients of 20 years of age or older. • With DXA, BMD deficits may be overestimated in patients with short stature, because they display a more severe decrease in bone area than in bone mineral content • For patients younger than 20 years of age whose height is at least 1 SD below age and sex matched healthy controls, BMD Z-scores should be adjusted for height or statural age to avoid overestimating deficits in BMD in people with short stature.
Outcomes	• Change in body bone mineral density (BMD) (adjusted for children) • Number of fractures • Quality of life (measured with CF-QOL or CFQR) Notes: • When reporting results, it is important to specify the machine make, model, and software version used, to enable comparison with other published data. • Z-scores are usually the most appropriate method in people with cystic fibrosis. The Z-score compares a measured BMD value to the average value obtained from a healthy population of the same sex and age as the patient. BMD is considered low in people with CF when the BMD Z-score in the spine or hip is lower than –2. However there are limitations to this approach, as all the BMD work is based on normal ranged in postmenopausal women, and we extrapolate this to CF patients, who of course are a much younger population.
Importance of outcomes	Critical outcome for decision making: • Change in body bone mineral density (BMD) (adjusted for children)
Setting	All settings in which NHS-commissioned health and social care is provided.

© NICE 2017. All rights reserved. Subject to Notice of rights.

Item	Details
Search strategy	Sources to be searched: Medline, Medline In-Process, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Cochrane Database of Abstracts of Reviews of Effectiveness, Health Technology Database, Embase. Limits (e.g. date, study design): Apply standard exclusions and English language filters. Supplementary search techniques: No supplementary search techniques were used. See appendix E.17 for full strategies
Review strategy	Appraisal of methodological quality: • The methodological quality of each prognostic study will be assessed using the checklist created by Hayden et al. (2013), as set out in the Developing NICE Guidelines Manual 2014. • The quality of the evidence for an outcome (i.e. across studies) will be assessed using adapted GRADE approach. Synthesis of data: • If comparative cohort studies are included, the minimum number of events per covariate to be recorded to ensure accurate multivariate analysis where possible. • Final and change scores will be pooled and if any study reports both, change scores will be used in preference over final scores. • If studies only report p-values from parametric analyses, and 95% CIs cannot be calculated from other data provided, this information will be plotted in GRADE tables, but evidence may be downgraded. • If studies only report p-values from non-parametric analyses, this information will be plotted in GRADE tables without downgrading the evidence, as imprecision cannot be assessed for non-parametric analyses • Review process: • A list of excluded studies will be provided following weeding. • Evidence tables and an evidence profile will be used to summarise the evidence.
Equalities	• Psychological and behavioural issues are more likely in people with a lower socioeconomic status. • Gender- outcomes are worse for women although there is no evidence that this is a consequence of difference in care. • Geographical issues – care is given through specialist centres and this may be a problem if a person with CF is living in an isolated location.
Notes/additional information	Bone mineral density in cystic fibrosis patients under the age of 18 years, 2008: http://www.ncbi.nlm.nih.gov/pubmed/18449130 2011 European cystic fibrosis bone mineralisation guidelines recommendation: • “In children, routine bone density scans should first be performed from around the age of eight to 10 years, and should be repeated approximately: every five years if the BMD Z-score is > −1; every two years if the Z-score is between −1 and −2; and every year if the Z-score is < −2 or if the child has experienced low trauma fractures. Bone density measurements can be first done at an earlier age and/or yearly in children with significant risk factors for low BMD and in children before prescribing specific treatments for low BMD.” • In adults with CF less than 50 years of age, routine bone density scans are recommended approximately: every five years if the BMD Z-score is > −1; every two years if the Z-score is between −1 and −2; every year if the Z-score is < −2. BMD measurements can be done yearly in adults with significant risk factors for low BMD. BMD measurements must be done before prescribing bone protective therapy. • In adults after 50 years of age, routine bone density scans are recommended approximately: every five years if the T-score is > −1; every two years if the T-

© NICE 2017. All rights reserved. Subject to Notice of rights.

Item	Details
	score is between −1 and −2.5; every year if the T-score is < −2.5. BMD measurements can be done yearly in adults with significant risk factors for low BMD. BMD measurements must be done before prescribing bone protective therapy" Bone densitometry in children assessed by dual x ray absorptiometry: uses and pitfalls: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1719622/pdf/v088p00795.pdf "It is suggested that performance of a DXA scan should be considered if a child has one of these conditions in conjunction with one of the following symptoms: low trauma or recurrent fractures, back pain, spinal deformity or loss of height, change in mobility status (for example, difficulty walking), or malnutrition" "given the difficulties discussed, a child may most appropriately act as his or her own control, with serial scans to monitor progress. Scan intervals of less than six months should only be considered in special situations such as monitoring the response to a pharmacological intervention, and for most patients annual scans should suffice". Relevant references: • Henderson RC, Madsen CD. Bone mineral content and body composition in children and young adults with cystic fibrosis. Pediatr Pulmonol 1999;27:80 – 4. • Cystic fibrosis-related bone disease in children: Examination of peripheral quantitative computed tomography (pQCT) data. http://www.ncbi.nlm.nih.gov/pubmed/25957706 • Bone mineral and body composition alterations in paediatric cystic fibrosis patients: http://link.springer.com/article/10.1007%2Fs00247-009-1446-8 • The prevalence of osteoporosis, osteopenia, and fractures among adults with cystic fibrosis: a systematic literature review with meta-analysis http://www.ncbi.nlm.nih.gov/pubmed/19949942 • A cross-sectional study of bone mineral density in children and adolescents attending a Cystic Fibrosis Centre. • Buntain 2004 Bone mineral density in Australian children, adolescents and adults with cystic fibrosis: a controlled cross sectional study. • Sermet-Gaudelus 2008 Low Bone Mineral Density in Young Children with Cystic Fibrosis.

© NICE 2017. All rights reserved. Subject to Notice of rights.