Institution: University of Sheffield

Unit of Assessment: 1 - Clinical Medicine

Title of case study: FRAX, an international tool for the assessment of fracture risk

1. Summary of the impact

Research at the University of Sheffield has resulted in FRAX, the first internationally-applicable fracture risk calculator that provides individualised 10-year probabilities of major osteoporotic fractures from readily available clinical risk factors. It has replaced bone mineral density (BMD) as the sole quantitative measure of fracture risk, thus increasing global access to risk assessment and improving targeting of treatment to patients at highest risk. FRAX is incorporated widely into national and international guidelines for osteoporosis management. Launched in 2008, it now provides country-specific calculations for 53 nations, in 28 languages. The online tool alone recently processed its 6.6 millionth calculation.

2. Underpinning research

The University of Sheffield has a worldwide reputation in the field of osteoporosis research, encompassing: epidemiology; diagnostic assessments; clinical outcome definitions including vertebral fracture; therapeutic developments; and health economics. In 1994, the WHO Collaborating Centre for Metabolic Bone Diseases at the University, led by Professor Kanis, published a WHO technical report establishing the working definition of osteoporosis based on dual x-ray absorptiometry (DXA) measurements of BMD (R1). This definition, the T-score threshold of -2.5, became and remains the international standard for the BMD diagnosis of osteoporosis. Originally intended as an epidemiological tool, it facilitated assessments of the prevalence and burden of osteoporosis across the world for the first time. Nationally and internationally, the T-score was subsequently incorporated into guidelines for the diagnosis and management of osteoporosis, adopted in many countries as a threshold for reimbursement of investigations and treatments; it also became widely used as a standard for recruitment of patients to studies of new therapies for osteoporosis.

Whilst osteoporosis remains operationally defined on the basis of the BMD T-score, it has long been recognised that the occurrence of fragility fractures, the hallmark of osteoporosis, is not dependent on BMD alone. Used in isolation, BMD lacks sensitivity for the prediction of future fractures (R2). Against this background, a research team within the WHO Collaborating Centre at Sheffield led a program of research in 1998 with the endorsement of the International Osteoporosis Foundation, the National Osteoporosis Foundation (USA), and the International Society for Clinical Densitometry and the American Society for Bone and Mineral Research. The core team was led by Professors Kanis and McCloskey (2003–date) in Sheffield, Professor Johnell in Malmo and Professor Anders Oden and Dr Helena Johansson in Gothenburg. The Collaborating Centre aimed to identify and validate clinical risk factors for use in fracture risk assessment on an international basis, either alone or in combination with BMD. A further aim was to incorporate suitably validated risk factors into algorithms for risk assessment that were sufficiently flexible to be used in the context of many primary care settings, including those where BMD testing was not readily available.

The research program necessitated the centralisation of individual level subject data from international cohorts, an achievement in itself that reflected the standing of the University of Sheffield in the global osteoporosis research community. The University of Sheffield and Professor McCloskey also contributed data from a large local cohort recruited to a concurrent MRC-funded study of fracture risk factors and prevention in elderly women (R3). The central collation of data, comprising approximately 250 000 subject-years of follow-up in 60 000 men and women with 5000 incident fractures, produced a unique dataset that allowed, for the first time, the examination of

several individual risk factors for fracture and their inter-relationships with other risk variables, notably age and BMD. The work gave rise to a series of well-received and highly cited meta-analyses, for example of the relationship between prior fracture and subsequent fracture (R4), culminating in a provisional fracture risk calculator. A subsequent validation study, undertaken in external cohorts comprised approximately 230,000 individuals with 1.2 million subject years of follow-up, including data from Sheffield (Professor Richard Eastell, 1995-date). The programme of work culminated with the launch of the online FRAX tool (www.shef.ac.uk/FRAX) in April 2008 with simultaneous publication of the UK (R5) and US (R6) FRAX tools.

3. References to the research

R1. (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser 843:1-129 (available at http://whqlibdoc.who.int/trs/WHO_TRS_843.pdf).

R2. Kanis JA (2002) Diagnosis of osteoporosis and assessment of fracture risk. Lancet 359:1929-1936 doi: 10.1016/S0140-6736(02)08761-5

R3. McCloskey EV, Beneton M, Charlesworth D, et al. (2007) Clodronate reduces the incidence of fractures in community-dwelling elderly women unselected for osteoporosis: results of a double-blind, placebo-controlled randomized study. J Bone Miner Res 22:135-141 doi: 10.1359/jbmr.061008

R4. Kanis JA, Johnell O, De Laet C, et al. (2004) A meta-analysis of previous fracture and subsequent fracture risk. Bone 35:375-382 doi: 10.1016/j.bone.2004.03.024

R5. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E (2008) FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 19:385-397 doi: 10.1007/s00198-007-0543-5

R6. Dawson-Hughes B, Tosteson AN, Melton LJ, 3rd, Baim S, Favus MJ, Khosla S, Lindsay RL (2008) Implications of absolute fracture risk assessment for osteoporosis practice guidelines in the USA. Osteoporos Int 19:449-458 doi: 10.1007/s00198-008-0559-5

4. Details of the impact

In the UK alone, osteoporosis results in more than 230,000 fractures, including 70,000 hip fractures, every year. Worldwide, it is projected that the burden of fractures will more than double by 2050, an increase that will be particularly marked in Asia. The need to identify high risk individuals for appropriate interventions has been recognised as a global health need.

Impact on skeletal health care in the UK and internationally

FRAX is the single most important development in osteoporosis management since the T-score definition in 1994 (also from the University of Sheffield) as it:

- Provides an estimate of absolute risk to inform physician and patient treatment choice.
- Provides an estimate of risk even in the absence of access to DXA technology (Dual-energy X-ray absorptiometry is a means of measuring bone mineral density) thus enfranchising management of osteoporosis in a wider community.
- Makes more effective use of DXA scanning resources.
- Permits targeting of therapy to highest risk individuals.
- Currently provides assessment of absolute fracture risk for the primary care community in 53 countries and 28 languages.
- Has been advocated by NICE in the UK and is incorporated into numerous national and international guidelines for osteoporosis.

Since the launch of FRAX in 2008, it has rapidly become the most internationally implemented and accepted risk calculator. It is most widely available as a free-to-use web-based calculator via the University of Sheffield website. The incorporation of a calculation counter (only activated by a complete risk calculation rather than a simple visit to the website) shows that approximately 6.6 million calculations had passed through the website since the counting tool was implemented on 1st June 2011 (accessed October 16th 2013) (S1). In addition to the web-based tool, FRAX is now incorporated into dual X-ray absorptiometry (DXA) scanner software, an iPhone app, standalone desktop tools and several paper-based calculators. In the UK, it is now available within the TPP SystmOne general practitioner software system, used by some 2000 GP practices currently with numbers growing. The impact of FRAX on the field of osteoporosis has been reflected in the rapid rise of FRAX-related publications. In the first year, 2008, there were only 11 FRAX-related publications but this increased to 60/year in 2009 and 2010, 95 in 2011 and 126 in 2012 (PubMed FRAX in title or abstract excluding Fragile X syndrome) (Accessed 13.22 Jan 23rd 2013).

Prior to FRAX, clinical decision making was largely based on a concept of high risk, based on factors such as prior fracture, age, low BMD etc., but it was not possible to actually quantify this risk and treatment was largely indicated by the finding of BMD-defined osteoporosis. This required a BMD scan in virtually all patients with a clinical risk factor without any prior assessment of their absolute risk. FRAX can now be used to more efficiently target BMD scans to those at or around an intervention threshold, an approach endorsed by NICE (S2), and thus improves resource use. The major beneficiaries of the FRAX research and development are men and women at highest risk of osteoporotic fracture. The reduction in the risk of fractures that results from well proven therapies is maximal in patients at highest risk with greater absolute risk reductions and reduced numbers needed to treat. The tool can also avoid or delay the need for therapy in patients previously deemed at high risk by the presence of low BMD (e.g. a BMD T-score of -2.5 in a 55 year old woman) but at low absolute risk; this improves the risk-benefit ratio of therapies given increasing concerns about potential complications of therapy such as osteonecrosis of the jaw or atypical femoral fractures.

To date, the use of FRAX has been endorsed in national/international guidance from the UK (S2), the US (S3), Canada (S4), Europe (S5), Switzerland, Japan, Austria and Sweden. In 2008, the National Osteoporosis Guideline Group launched a website twinned to the UK FRAX model that gave guidance for the use of FRAX results in individuals to guide further assessment (e.g. DXA scanning) or intervention (www.shef.ac.uk/NOGG). This guideline was endorsed by many national societies including the Royal College of Physicians, Royal College of General Practitioners, Primary Care Rheumatology Society, British Geriatrics Society, British Orthopaedic Association, Bone Research Society and patient societies including the National Osteoporosis Society, Osteoporosis Dorset and Osteoporosis2000. It has recently been updated. In the UK, the recently published NICE Clinical Guideline endorsed the use of FRAX as one of two risk calculators that should be used to target the use of dual X-ray absorptiometry (DXA) scans (NICE CG146) (S2) and it has been incorporated in the NHS Map of Medicine for osteoporosis, which aims to inform patient choice (S6).

In 2010, The International Society for Clinical Densitometry (ISCD) and the International Osteoporosis Foundation (IOF) convened a FRAX Position Development Conference (PDC) resulting in guidelines on the interpretation and use of FRAX in clinical practice (S7). In 2011, the US Preventive Service Task Force (USPSTF) recommended the use of FRAX to calculate the 10-year risk for osteoporotic fractures to guide screening decisions for women younger than 65 years (S8). In Europe in 2012, FRAX has been incorporated into guideline development documents for the management of osteoporosis in postmenopausal women as well as glucocorticoid-induced osteoporosis in men and women.

5. Sources to corroborate the impact

S1. www.shef.ac.uk/FRAX

S2. Osteoporosis: assessing the risk of fragility fracture. NICE Clinical Guideline CG146 (Issued: August 2012) (http://tinyurl.com/nck8c4l).

S3. National Osteoporosis Foundation 2013 Clinician's guide to prevention and treatment of osteoporosis (http://tinyurl.com/nu29v8t) Page 22 corroborates the recommendation to use FRAX as well as its translation to US norms.

S4. Papaioannou A, Morin S, Cheung AM, Atkinson S, Brown JP, Feldman S, Hanley DA, Hodsman A, Jamal SA, Kaiser SM, Kvern B, Siminoski K, Leslie WD for the Scientific Advisory Council of Osteoporosis Canada. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. CMAJ 2010. doi: 10.1503/cmaj.100771 Page 3 corroborates recommendation of FRAX validated in Canadians.

S5. Endorsement of FRAX in Europe: A framework for the development of guidelines for the management of glucocorticoid-induced osteoporosis (http://tinyurl.com/ou4dgdx).

S6. NHS Choices Map of Medicine (http://tinyurl.com/k9ycnfk).

S7. ISCD/IOF (http://tinyurl.com/k2zs6xq).

S8. U.S. Preventive Services Task Force. Screening for Osteoporosis 2011 (http://tinyurl.com/6fb6zfp).