

Institution: University of Sheffield		
Unit of Assessment: A-01 Clinical Medicine		
Title of case study: FRAX – Identification and treatment of patients at high risk of osteoporotic fractures		
Period when the underpinning research was undertaken: 2010–2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Eugene McCloskey	Professor in Adult Bone Disease	1985–present
Period when the claimed impact occurred: 2013–2020		
Is this case study continued from a case study submitted in 2014? N		
<p>1. Summary of the impact (indicative maximum 100 words)</p> <p>FRAX, developed by the University of Sheffield, is the most widely adopted fracture prediction tool globally. Since 2014, usage has increased by 32% with incorporation in over 120 guidelines worldwide. In the setting of population screening for fracture risk, three recently published randomised controlled trials of FRAX-based approaches and a subsequent meta-analysis have shown a 20% reduction in hip fractures, with excellent cost-effectiveness. Awareness of high fracture risk has increased treatment uptake in patients. Global use of FRAX enabled the study of the impact of COVID-19 on non-communicable disease care and permitted the early recovery of risk assessments in many healthcare settings.</p>		
<p>2. Underpinning research (indicative maximum 500 words)</p> <p>The personal and societal burden of osteoporotic (low-trauma) fractures is substantial and increasing. In 2010, 3.5 million new fragility fractures were sustained in the EU, including 620,000 hip fractures. The economic burden, estimated at €37 billion, will increase by 25% by 2025; importantly, the majority of individuals at high risk of fracture remain untreated. The University of Sheffield, with a worldwide reputation in the field of osteoporosis clinical research, established the working definition of osteoporosis based on measurements of bone mineral density (BMD) in 1994. In 2008, McCloskey and colleagues at the University launched a freely available online fracture risk assessment tool (FRAX - http://www.shef.ac.uk/FRAX) representing another paradigm shift in osteoporosis management: the movement away from treatment based on BMD alone towards that based on absolute fracture risk. The initial development and impact of FRAX was submitted in REF2014, but significant and novel developments have occurred since July 2013 as described below.</p> <p>A key component of FRAX was that the risk identified should be at least partly reversible by treatments that modify bone mass through effects on bone turnover. Post hoc analyses of phase III randomised clinical trials had previously shown that patients with high risk of fracture by FRAX were responsive to treatment with antiresorptive medications (e.g. denosumab); subsequent post hoc analyses showed that FRAX-identified high risk patients also responded to anabolic therapies (e.g. teriparatide, abaloparatide, romosozumab). The most important UK development was completion and publication of a large MRC- and Versus Arthritis-funded UK study which asked whether a community-based screening programme, based on FRAX hip fracture probability, could reduce fractures in older women (the SCOOP study) [R1]. This</p>		

prospective randomised controlled trial, comprising almost 12,500 women aged 70-85 years at 7 centres, demonstrated that the FRAX-based screening program increased the uptake of osteoporosis medications in women at high risk [R2] and reduced the incidence of hip fractures by 28% compared to standard care; if extrapolated to the UK, at least 8,000 hip fractures could be prevented annually in the UK [R3]. The approach was demonstrated to be highly cost-effective [R4].

The two other independent studies also examined the use of FRAX-based screening programs in Denmark and the Netherlands. In a group with similar characteristics to the participants of the SCOOP trial, the Danish study showed a 17% reduction in hip fractures [R5]. The study group in the Netherlands conducted a recent meta-analysis of all three trials comprising a total number of 42,009 participants [R6]. In the screening arms, only 11-18% of the participants were categorised at high risk and started medication. This targeted intervention, however, showed a statistically significant and clinically relevant reduction of major osteoporotic fractures (HR = 0.91; 95%CI = 0.84–0.98) and hip fractures (HR = 0.80; 95%CI = 0.71–0.91). The number needed to treat to prevent one hip fracture was 28. The authors concluded that implementation of screening in older women should be considered a serious option to prevent osteoporotic fractures, especially hip fractures.

3. References to the research (indicative maximum of six references)

University of Sheffield researchers in **bold**

- R1.** Shepstone, L., E. Lenaghan, C. Cooper, S. Clarke, R. Fong-Soe-Khioe, R. Fordham, N. Gittoes, I. Harvey, N. Harvey, A. Heawood, R. Holland, A. Howe, **J. Kanis**, T. Marshall, T. O'Neill, T. Peters, N. Redmond, D. Torgerson, D. Turner, **E. McCloskey** (2018). "Screening in the community to reduce fractures in older women (SCOOP): a randomised controlled trial." *The Lancet*. 391(10122), 741-747. [https://doi.org/10.1016/S0140-6736\(17\)32640-5](https://doi.org/10.1016/S0140-6736(17)32640-5).
- R2.** Parsons, C. M., N. Harvey, L. Shepstone, **J. A. Kanis**, E. Lenaghan, S. Clarke, R. Fordham, N. Gittoes, I. Harvey, R. Holland, N. M. Redmond, A. Howe, T. Marshall, T. J. Peters, D. Torgerson, T. W. O'Neill, **E. McCloskey**, C. Cooper (2019). "Systematic screening using FRAX((R)) leads to increased use of, and adherence to, anti-osteoporosis medications: an analysis of the UK SCOOP trial." *Osteoporosis International* 31(1), 67-75. <https://doi.org/10.1007/s00198-019-05142-z>.
- R3.** **McCloskey, E.**, H. Johansson, N. C. Harvey, L. Shepstone, E. Lenaghan, R. Fordham, I. Harvey, A. Howe, C. Cooper, S. Clarke, N. Gittoes, A. Heawood, R. Holland, T. Marshall, T. W. O'Neill, T. J. Peters, N. Redmond, D. Torgerson, **J. A. Kanis** (2018). "Management of Patients With High Baseline Hip Fracture Risk by FRAX Reduces Hip Fractures-A Post Hoc Analysis of the SCOOP Study." *Journal of Bone and Mineral Research*. 33(6), 1020-1026. <https://doi.org/10.1002/jbmr.3411>.
- R4.** Turner, D. A., R. F. S. Khioe, L. Shepstone, E. Lenaghan, C. Cooper, N. Gittoes, N. C. Harvey, R. Holland, A. Howe, **E. McCloskey**, T. W. O'Neill, D. Torgerson, R. Fordham (2018). "The Cost-Effectiveness of Screening in the Community to Reduce Osteoporotic Fractures in Older Women in the UK: Economic Evaluation of the SCOOP Study." *Journal of Bone and Mineral Research* 33(5), 845-851. <https://doi.org/10.1002/jbmr.3381>.
- R5.** Rubin, K. H., M. J. Rothmann, T. Holmberg, M. Hoiberg, S. Moller, R. Barkmann, C. C. Gluer, A. P. Hermann, M. Bech, J. Gram and K. Brixen (2018). "Effectiveness of a two-

step population-based osteoporosis screening program using FRAX: the randomized Risk-stratified Osteoporosis Strategy Evaluation (ROSE) study." *Osteoporosis International*. 29(3), 567-578. <https://doi.org/10.1007/s00198-017-4326-3>.

- R6.** Merlijn, T., Swart, K. M. A., van der Horst, H. E., Netelenbos, J. C., Elders, P. J. M. (2020). "Fracture prevention by screening for high fracture risk: a systematic review and meta-analysis." *Osteoporosis International*, 31(2), 251-257. <https://doi.org/10.1007/s00198-019-05226-w>.

4. Details of the impact (indicative maximum 750 words)

The principal beneficiaries of FRAX are patients who are enabled to receive necessary, or avoid unnecessary, treatment to reduce fracture risk. The tool, integrated with guidelines, provides healthcare professionals with a rational approach to targeting osteoporosis interventions within a wide variety of healthcare systems.

Impact on patient management

Globally, the FRAX website shows year-on-year growth from 1,915,584 usage sessions in 2015 to 2,532,606 sessions in 2019, a 32% increase [S1]. Each session represents management of at least one patient within that session. By 2016, uptake of FRAX in clinical practice was reflected by its inclusion and/or endorsement in 120 clinical guidelines worldwide [S2]. In 2017, NICE accredited the FRAX-based National Osteoporosis Guideline Group's (NOGG) thresholds for interventions with osteoporosis medications in the UK [S3, S4]. NOGG provides a direct link between the UK FRAX tool and patient management decisions. Between 2008 and 2014, 488,585 sessions were accessed on the NOGG site, but between 2014 and 2019, this had more than doubled to 981,007 sessions. In an analysis of annual FRAX and NOGG website access published in 2017, there were a total of 348,964 and 208,766 sessions on the FRAX and NOGG websites respectively from UK-based users [S5]. Almost all (95.7 %) of the NOGG website sessions arose from calculations being passed through from FRAX; of these, 74.5% of FRAX calculations were in patients without a bone mineral density (BMD) measurement, confirming clinicians were using FRAX in accordance with the 2017 NICE guidance.

In the context of secondary prevention of fractures, in 2017 the Royal College of Physicians reported a Fracture Liaison Service (FLS) audit comprising 18,356 patients with fracture in 38 FLS. It found that 35% of all patients, and 42% of those aged below 75, were assessed using FRAX or QFracture as part of their management pathway, suggesting good uptake of NICE guidance [S6].

The SCOOP study in the UK demonstrated that screening using FRAX hip fracture probabilities was associated with a highly clinically significant decrease in hip fracture incidence (28%). Of those participants in the screening arm identified to be at high fracture risk, 75.8% were taking osteoporosis medication by 6 months into the study compared with only 2.0% in the control arm overall [S7]. By 60 months, 56.6% of those identified at high risk of fracture reporting taking medication, compared with 9.7% in the control arm overall. Informing the patient and GP thus had a marked impact on prescribing of treatment and adherence.

In 2018, the United States Preventive Services Task Force (USPSTF) recommended that women under 65 are screened for fracture risk (by various tools including FRAX) and those judged high risk are treated; the effect is to reduce the use of limited BMD resources in younger post-menopausal women [S8].

Increasing global reach of FRAX

In 2014, the FRAX tool catered for 53 nations and 28 languages, and in 2020 it has provided calibrated models for 73 nations and 35 languages. In 2015, it was estimated that the tool provided coverage for fracture risk assessment in more than 79% of the global population. Since REF2014, the FRAX website tool has provided a further 24.8 million calculations globally as of 23 November 2020, with over 31 million calculations in the last 9.5 years [S9]. It should be noted that this is an underestimate as only calculations entered directly to the website are counted. FRAX is also available on densitometric equipment worldwide, on iPhone, and as paper-based models. Recently, access to the tool has been embedded in the electronic patient record system of the Mayo Clinic in the US, an approach that will be increasingly important going forward [S10]. In 2020, FRAX was CE-marked as a Class 1 medical device.

FRAX and the COVID-19 pandemic

The daily usage of FRAX globally, captured via the website, has also enabled examination of the impact of the COVID-19 pandemic on osteoporosis management worldwide [S11]. Compared to February 2020, global access to FRAX in April 2020 was reduced by 58.3%. There were smaller reductions in Asia than elsewhere, partly related to earlier and less-marked nadirs in some countries (e.g. China, Taiwan). In Europe, the majority of countries (24/31, 77.4%) reduced usage by at least 50%. In the UK, the decrease in FRAX usage (65%) was not as marked or prolonged as the interruption in access to BMD services (practically 100% decrease as units closed April-June 2020) reflecting the continuing ability to assess fracture risk without bone density. More recent follow-up shows a good recovery in FRAX usage [S1].

5. Sources to corroborate the impact (indicative maximum of 10 references)

- S1. Brief report on FRAX and NOGG website access from UK 2015-2020.
- S2. Systematic review of inclusion of FRAX in guidelines. Kanis, J. A., Harvey, N. C., Cooper, C., Johansson, H., Odén, A., & McCloskey, E. V. (2016). A systematic review of intervention thresholds based on FRAX. *Archives of Osteoporosis*, 11(1), 25. <https://doi.org/10.1007/s11657-016-0278-z>.
- S3. National Osteoporosis Guideline with NICE accreditation (granted 2017) (<https://www.sheffield.ac.uk/NOGG/index.html>).
- S4. NICE Quality Standard (QS149) April 2017 (<https://www.nice.org.uk/guidance/qs149>). Adoption of NOGG intervention thresholds by NICE Guidance.
- S5. Review of access to FRAX and NOGG. McCloskey, E. V., Johansson, H., Harvey, N. C., Compston, J., & Kanis, J. A. (2016). Access to fracture risk assessment by FRAX and linked National Osteoporosis Guideline Group (NOGG) guidance in the UK—an analysis of anonymous website activity. *Osteoporosis International*, 28(1), 71–76. <https://doi.org/10.1007/s00198-016-3696-2>.
- S6. RCP FLS Audit, April 2017 <https://www.hqip.org.uk/wp-content/uploads/2018/02/fracture-liaison-service-database-fls-db-clinical-audit-report-april-2017.pdf>.
- S7. Paper on impact of screening by FRAX on medication uptake in SCOOP. Parsons, C. M., Harvey, N., Shepstone, L., Kanis, J. A., Lenaghan, E., Clarke, S., Fordham, R., Gittoes, N., Harvey, I., Holland, R., Redmond, N. M., Howe, A., Marshall, T., Peters, T. J.,

Torgerson, D., O'Neill, T. W., McCloskey, E., & Cooper, C. (2019). Systematic screening using FRAX® leads to increased use of, and adherence to, anti-osteoporosis medications: an analysis of the UK SCOOP trial. *Osteoporosis International*, 31(1), 67–75. <https://doi.org/10.1007/s00198-019-05142-z>.

- S8.** US Preventive Services Task Force Final Recommendation Statement: *Osteoporosis to Prevent Fractures: Screening*, June 2018. <https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/osteoporosis-screening1>
- S9.** Screenshot (as PDF, appendix 2) of the FRAX homepage on 23rd November 2020. The calculator has recently surpassed 31 million calculations via the website since June 2011 (www.shef.ac.uk/FRAX). By visiting the website, and clicking on the different calculation tools, the global coverage of FRAX can be envisaged.
- S10.** 2015 article from the Mayo Clinic describing the use of FRAX risk assessment tool. <https://www.mayoclinic.org/medical-professionals/endocrinology/news/new-tools-to-predict-fracture-risk/mac-20430573>.
- S11.** Access to FRAX as a marker of the impact of COVID-19 on non-communicable disease management worldwide. McCloskey, E. V., Harvey, N. C., Johansson, H., Lorentzon, M., Vandenput, L., Liu, E., & Kanis, J. A. (2020). Global impact of COVID-19 on non-communicable disease management: descriptive analysis of access to FRAX fracture risk online tool for prevention of osteoporotic fractures. *Osteoporosis International*, 32(1), 39–46. <https://doi.org/10.1007/s00198-020-05542-6>