Institution: University of Cambridge		
Unit of Assessment: UOA1		
Title of case study: New diagnostics and treatment of severe osteoporosis.		
Period when the underpinning research was undertaken: Feb 2005 – April 2017		
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:**
Ken Poole	Reader in Metabolic Bone Diseases	May 2007 – present
Graham Treece	Reader in Information Engineering	Oct 2003 – present
Andrew Gee	Reader in Engineering	Oct 2001 – present
Juliet Compston	Professor of Bone Medicine	Oct 2003 – Dec 2011 Jan 2005 – Sep 2010
Jonathan Reeve	Director of Research	Nov 2010 –Feb 2012
Period when the claimed impact occurred: Jan 2014 – present		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact (indicative maximum 100 words)

Every three seconds someone in the world breaks a bone because of osteoporosis – a disease in which bones become thin and porous. Osteoporotic fractures cost the UK around GBP4,500,000,000 each year, with hip fractures alone accounting for 69,000 emergency admissions into English hospitals. Cambridge University research and advisory work has underpinned the development of a novel treatment and diagnostics that have transformed the management of osteoporosis. These include the development of romosozumab, a major new therapeutic, which prevents osteoporotic fractures by blocking the bone protein sclerostin (Europe-wide approval, 2019), and the use of femoral Quantitative Computed Tomography for diagnosing osteoporosis (incorporated in the FRAX online fracture risk calculator used by 66 countries worldwide).

2. Underpinning research (indicative maximum 500 words)

Osteoporosis affects >3,000,000 people in the UK (Svedborn A et al, *Arch Osteoporos 2013; 8;137*); weakening bones and leading to painful, deforming fractures of the vertebrae and hips. It is difficult to detect and usually diagnosed only after a patient develops their first 'fragility' fracture (bones that break after falling from standing height or less). More than 500,000 people receive hospital treatment for fragility fractures every year as a result of osteoporosis (Svedborn et al.).

Mapping of sclerostin in human bone: Sclerostin is a secreted glycoprotein produced primarily by osteocytes – cells that control the balance of bone resorption and formation through a network of tiny channels in the human skeleton. In February 2005, Cambridge University researchers mapped site-specific changes in sclerostin expression in mineralised human bone and showed for the first time that sclerostin is deposited throughout bone channels, preventing new bone from filling-in these cavities. This research identified sclerostin as the major physiological inhibitor of human bone owing to its location within mineralised bone. It further showed that osteocytes control surface bone formation by the timely secretion of this 'master' inhibitory signal [1]. This Cambridge-led research contributed directly to the development of the anti-sclerostin antibody 'romosozumab' as a therapy of osteoporosis (see below). The pivotal clinical trial sponsored by Amgen showed that romosozumab treatment results in the production in one year of the same amount of bone as that lost through 10 years of normal ageing. It rapidly prevents patients from fracturing their vertebrae, lowering the risk of new vertebral fractures by 75% relative to placebo (Cosman F et al, *N Engl J Med* 2016; 375:1532-43).

Developing sclerostin-directed therapies of osteoporosis: Poole and the Cambridge team also developed leading expertise in the use of bone imaging to measure the efficacy of anti-osteoporosis drugs [2-4]. Therefore in 2013, Amgen commissioned the team to study the effects of monthly romosozumab therapy in a placebo-controlled trial of 56 women. Analysis of the spinal Computed Tomography (CT) scans of these patients using a novel 3D cortical bone mapping

(CBM) software developed together with Cambridge University engineers, showed that romosozumab therapy had superior effectiveness over alternative bone agents, increasing vertebral thickness – a common site of osteoporotic crush or wedge fractures – by 12% and density by 22% [5]. These findings were subsequently confirmed in a separate study that showed romosozumab treatment is associated with a 48% lower risk of new vertebral fractures than the standard treatment, alendronate (Saag KG et al*. N Engl J Med* 2017; 377:1417-27*)*

Developing novel imaging approaches to diagnose osteoporosis on routine CT scans: Osteoporosis is usually not detected until patients present with painful fractures. Earlier detection offers the opportunity for intervention, treating patients before fractures develop or progress. Cambridge imaging research was critical in testing, validating and implementing Quantitative Computed Tomography (QCT), a method to diagnose osteoporosis in routine clinical practice. QCT measures bone mineral density (BMD) using a standard CT scanner that can convert the tomographic image data to BMD values. QCT (also called Mindways QCT Pro) is used primarily to evaluate BMD at the lumbar spine and hip and to guide treatment decisions. In 2015, Cambridge University medical and engineering researchers analysed a series of clinical trials involving 10 sites and 1,201 patients sampled from 11,178 volunteers. Together with Mindways software professionals and academic triallists in the USA, Iceland and Czech Republic, they showed that QCT-BMD measurement accurately predicts hip fractures in healthy women and men [6-8]. In 2017 the new diagnostic method was incorporated into UK National Osteoporosis Guidelines [9].

Deploying 3D bone imaging to understand the mode of action of new osteoporosis therapies: As well as diagnosing latent osteoporotic fractures, in 2009 Cambridge researchers applied their patented 3D CBM software [10] to discover the precise bone-building effects of the two drugs used to treat severe osteoporosis: teriparatide injectable parathyroid hormone therapy, and denosumab, an anti-RANKL antibody. This research has enabled drug development teams to determine precisely where new bone is formed following treatment with teriparatide, romosozumab and denosumab [2-5] as well as in response to high intensity exercise regimens. Of particular note, in 2015 this research showed that denosumab increases bone density in defective areas of the hip in women with osteoporosis, preventing hip fracture and providing evidence of drug efficacy [2].

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

Evidence of research quality: *Research published in peer-review journals. Research was supported by competitively won grants.

*[1] Poole KE, van Bezooijen RL, Loveridge N, Hamersma H, Papapoulos SE, Lowik CW, **Reeve J**. Sclerostin is a delayed secreted product of osteocytes that inhibits bone formation. *FASEB journal*: official publication of the Federation of American Societies for Experimental Biology. 2005;19(13):1842-4 *.

*[2] **Poole KES, Treece GM, Gee AH**, Brown JP, McClung MR, Wang A, et al. Denosumab Rapidly Increases Cortical Bone in Key Locations of the Femur: A 3D Bone Mapping Study in Women With Osteoporosis. *Journal of Bone and Mineral Research*. 2015;30(1):46-54 *.

*[3] **Treece GM**, **Gee AH**, Mayhew PM, **Poole KE**. High resolution cortical bone thickness measurement from clinical CT data. *Med Image Anal*. 2010;14(3):276-90 *.

*[4] Whitmarsh T, **Treece GM, Gee AH, Poole KE**. Mapping Bone Changes at the Proximal Femoral Cortex of Postmenopausal Women in Response to Alendronate and Teriparatide Alone, Combined or Sequentially. *J Bone Miner Res*. 2015; 30(7):1309-18 *.

*[5] **Treece G, Gee A**. Cortical Bone Mapping: Measurement and Statistical Analysis of Localised Skeletal Changes. *Current osteoporosis reports*. 2018;16(5):617-25 *.

*[6] **Poole KES,** Skingle L, **Gee AH**, Turmezei TD, Johannesdottir F, Blesic K.. **Reeve, J, Treece GM**. Focal osteoporosis defects play a key role in hip fracture. *Bone.* 2017;94:124-34 *.

*[7] **Treece GM**, **Gee AH**, Tonkin C, Ewing SK, Cawthon PM, Black DM, et al. Predicting Hip Fracture Type With Cortical Bone Mapping (CBM) in the Osteoporotic Fractures in Men (MrOS) Study. *Journal of Bone and Mineral Research*. 2015;30(11):2067-77 *.

*[8] Johannesdottir F, **Poole KES**, **Reeve J**, Siggeirsdottir K, Aspelund T, Mogensen B, et al. Distribution of cortical bone in the femoral neck and hip fracture: A prospective case-control analysis of 143 incident hip fractures; the AGES-REYKJAVIK Study. *Bone*. 2011;48(6):1268-76 *.

ortical Bone Mapping: Measurement and Statistical Analysis of Localised Skeletal Changes
[9] **Compston, J**., Cooper, A., Cooper, C., Gittoes, N., Gregson, C., Harvey, N., Hope, S., Kanis, J. A., McCloskey, E. V., **Poole, K**., Reid, D. M., Selby, P., Thompson, F., Thurston, A., Vine, N., & National Osteoporosis Guideline Group (NOGG) (2017). UK clinical guideline for the prevention and treatment of osteoporosis. *Archives of osteoporosis*, *12*(1), 43. https://doi.org/10.1007/s11657-017-0324-
[10] **Patent**: **Graham Treece** and **Ken Poole** (Inventors), Accurate cortical thickness measurement from clinical CT data GB0917524.1. A method of determining the cortical thickness of a patient's bone, 2009. International (PCT) Patent Application No PCT/GB2010/051671, CU ref: TRE-2326-09-01, International search ref: PC925159WO. 5

Competitive grant funding

04/2013-03/2014 NHS Innovation fund, GBP26,778, PI **Ken Poole**
09/2015-08/2017 Cambridge University Hospitals NHS Foundation Trust innovation award and Addenbrooke's Charitable Trust Feasibility award, GBP35,643, PI **Ken Poole**
09/2018-03/2022 NIHR Research for Patient Benefit grants, GBP244,396 + GBP33000 PI **Ken Poole**
04/2017-03/2022 Institutional Award: NHS NIHR Biomedical Research Centre Metabolism, Endocrinology and Bone, GBP500,578, Sub-theme Lead **Ken Poole** and Lead Professor S Farooqi.
2017-2022 Industry funding (Lilly, Amgen Inc.) to the Departments of Engineering and Medicine, GBP440,499, PI **Ken Poole**

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

Over 3,000,000 people in the UK have osteoporosis, leading to 500,000 fragility fractures each year. Vertebral, hip and other osteoporotic fractures are estimated to cost the UK around GBP4,500,000,000 each year, with hip fractures alone accounting for 69,000 emergency admissions into English hospitals (Source: National Institute for Health and Care Excellence, '*Falls and fragility fractures', 2018*). Many of these fractures could be prevented with earlier intervention. The pain and deformity of osteoporotic vertebral fractures accounts for an additional 14 GP visits in the year after the injury [A]. Once diagnosed, treatment for osteoporosis is both clinically and cost-effective for preventing more fractures. Improving the identification of vertebral fractures and osteoporosis is critical to reducing these enormous medical and fiscal costs [A].

Impact on the health and wellbeing of people

Romosozumab* (EVENITY™) *treatment has improved health and wellbeing of women with severe osteoporosis: Since romosozumab was first produced in 2005, Ken Poole has provided 15 years of expert advice to the drug companies co-developing the drug; UCB (Union Chimique Belge) and Amgen. The Executive Vice-President of UCB described Poole's research and expert advice as *'valuable and critical…in the recent EU regulatory process which has led to the Committee for Medicinal Products for Human Use (CHMP) positive opinion regarding romosozumab*' [B]**.** This filing culminated in approval of romosozumab by the European Medicine's Agency (EMA) and Federal Drug Administration (FDA, USA) in 2019. Romosozumab is now being used to treat >60,000 patients across the world including in Europe, USA, Japan, Canada and Australia [B, C]. Extrapolating the numbers of fractures prevented during the pivotal trial (Saag KG, et al*. N Engl J Med.* 2017) to these 60,000 women provides an estimate of the impact of romosozumab on women's health globally. Within one year of starting romosozumab instead of alendronate, 1,123 fewer vertebral fractures and 611 fewer hip fractures are expected to have occurred. Romosozumab increased cortical thickness by 10.3%± 4.9 over 12 months; a significant ($p \leq 0.05$) increase over the next best treatment, teriparatide, which increased cortical thickness 4.3% ± 3.4 [D]. Hisoko N. from Kyoto, Japan was pleased to benefit, *"When my 88-year-old mother fell and fractured her spine, we feared she would stay bedridden for life. Thankfully, her doctor prescribed EVENITY®. After several months of treatment, her bone mineral density has increased and her risk for another fracture has been greatly reduced"* [E]

Impact on practitioners and the delivery of professional services

An improved tool was developed to diagnose osteoporosis in the clinic: QCT Pro devices – new effective tools for diagnostic discordance of osteoporosis – have been used worldwide [text

removed for publication]. [F]. Cambridge University research was critical for the approval of the QCT Pro method to diagnose osteoporosis in routine clinical practice [6-8], via the International Society of Clinical Densitometry (ISCD) official position statement [G] which cited five papers from the University of Cambridge. A further health impact of improved diagnosis occurred as QCT Pro measurements of bone density were then incorporated into FRAX, the online fracture risk prediction tool and App. Developed by Sheffield University, FRAX evaluation of fracture risk was restricted to clinical risk factors and hip bone density values alone hip (from Dual-energy X-ray Absorptiometry, DXA) [H]. With the introduction of QCT Pro, FRAX now has the facility, in 66 countries worldwide, to calculate patient risk estimates from QCT Pro measurements of bone density as well as DXA [H]. Dr Brown, President of Mindways QCT Pro commented, "*Your work demonstrating superiority of QCT-based hip measurements to DXA-based hip measurements for assessment of hip fracture risk assessment has been pivotal in obtaining recognition within ISCD position statements of the clinical utility of QCT-based assessments of the hip in predicting hip fracture risk."* [F].

Improved care of osteoporosis patients in the Cambridgeshire regional referral centre: In 2016 with the support of an NHS Innovation Award, the Cambridge team established the QCT Pro Opportunistic Osteoporosis Screening Service at Cambridge University Hospitals. This service, endorsed by the Clinical Director of Radiology [I], deploys routine clinically acquired medical CT scans to diagnose osteoporosis as an 'added-extra' to mitigate the devastating effect of late diagnosis. Automated letters are then sent to patients' GPs to give specific advice on treating osteoporosis to prevent future fractures. The service was audited in 2019 [I] and showed that 581 patients had been detected and benefited from specific osteoporosis intervention. A meta-analysis of fracture risk found that treatment of 28 high-risk individuals would prevent one hip fracture in that population (Merlijn T. et. al. *Osteoporosis Int.* 2020; 31;251: 257). Accordingly, the service is estimated to have prevented 20 hip fractures, preserving people's health and wellbeing. Similarly, vertebral fracture detection rates increased from 10-30% in 2013 to 79% in 2018 through local audits [I]. This service is now being tested across the Eastern region in other NHS hospitals including Bury St Edmunds, Peterborough, Huntingdon and Bedford. The benefit of implementing this service was explained by one patient, a retired engineer: "*During my annual bowel CT check-up in December 2019 I was found to have severe osteoporosis in my spine and hips. I am so grateful that this was picked up and treated before any damage occurred. I know all too well the agony of spine fractures having broken a lumbar vertebra falling from a ladder some years ago*" [I]. Patients suffering from the intense pain of osteoporotic vertebral fractures are often left unable to work and may need years of therapy during recovery (Al-Sari *et al. Osteoporosis Int*. 2016; 27: 2891*)*. Improved osteoporosis care not only reduces the risk of osteoporotic fractures but also could reduce osteoporosis-related health care costs (by for example reducing hip fractures, which cost health and social services over GBP1,000,000,000 each year – National Hip Fracture Database 2019 annual report). The 2019 Royal Osteoporosis Society Bone Academy Patient Insight Survey showed that 92.5% of respondents (n=7,237) with osteoporosis considered a programme of opportunistic detection of osteoporosis using CT to yield either 'extremely beneficial' (70%) or 'very beneficial' (22.5%) outcomes for patients [I].

Impact on commerce and the economy

Romosozumab. Since Romosozumab launched in May 2019, Amgen has generated revenue of USD189,000,000 to year-end 2019 [E]. Over 60,000 women have received romosozumab for severe osteoporosis worldwide, at an average wholesale price of USD26,243 for 12 months [B], equating to approximately USD13,000,000 in sales.

QCT Pro diagnostic software. Screening for osteoporosis is estimated to have reduced Cambridgeshire hip fracture-associated costs by GBP283,260 (GPB14,163 for each of 20 fractures averted from Leal *et al*. *Osteoporosis Int.* 2016; 27:549*)* versus screening costs and the annual treatment costs.

Cortical Bone Mapping. The Lilly-commissioned Cambridge CBM research programme allayed growing clinical concerns that teriparatide treatment for osteoporosis might worsen hip strength. The research demonstrated the converse; that hip 3D structure improved substantially after

treatment with teriparatide for 18-24 months. Cambridge CBM hip maps subsequently featured in product literature to reassure prescribers worldwide, aiding commercial sales [4]. Teriparatide had US sales of USD1,800,000,000 in 2018. In osteoporotic women, Cambridge CBM research found that denosumab (a monoclonal antibody used to treat osteoporosis in >80 countries worldwide) enhanced bone accrual in parts of the hip that commonly break during a fall to the side [2], enhancing claims of drug efficacy. Denosumab had combined worldwide net sales of USD3,200,000,000 in 2016 [J].

Impact on pharmaceutical education strategy: Testimonials from the Head of Bone, at Lilly and Head of Bone at Amgen & UCB describe how Cambridge CBM research has influenced understanding, learning and pharmaceutical strategy [K]. With drugs that add new bone structure or mineral, it is important to discover where and how much new bone is formed. The research identified the treatment effects of denosumab, teriparatide and romosozumab [2-5] which had impacts on physician understanding and learning, and in turn prescribing of the drugs. Teriparatide CBM results allowed Lilly to reassure prescribers using CBM images in prescriber handouts to show precisely where bone accrual was occurring with the drug [L]. This allowed the pharmaceutical industry to educate prescribers on the benefits of denosumab and teriparatide on preventing fractures through targeted bone accrual at sites of known vulnerability. The testimonial from Amgen describes how the Cambridge research has influenced educational strategy: *"The work has also been used in education initiatives, not only by Amgen but I have witnessed related work by other pharmaceutical companies to understand and educate practitioners on the effects of bone anabolic treatments"* [K].

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

[A] Royal Osteoporosis Society Vertebral Fracture Guidelines, pages 3,4,5

[B] UCB Evidence: (i) Testimonial, Executive Vice President, UCB (ii) UCB press releases: EVENITY® (romosozumab) Treatment of Severe Osteoporosis in Postmenopausal Women at High Risk of Fracture, October 18, 2019, page 1

[C] Romosozumab authorisation: (i) EMA authorisation October 2019 (ii) FDA approval April 2018 (iii) Correspondence with UCB regarding Evenity prescriptions.

[D] Poole, K Treece, G et al, Romosozumab enhances vertebral bone structure in women with low bone density, with larger gains in cortical and endocortical bone evident at one year compared with teriparatide or placebo. Table 2. *(data on file, Amgen).*

[E] Amgen Inc. (i) Patient testimonial: 2019 Amgen Inc Annual Letter to Shareholders page 5 (ii) Romosozumab sales figures, Amgen Inc Form 10-K 2019, page 52

[F] Mindways QCT Pro: (i)Testimonial, President, Mindways Software (ii) Mindways QCT correspondence containing device numbers & global distribution (iii)FDA Approval for marketing of hip QCT technology, August 2014.

[G] ISCD 2015 ISCD Position Statement on Advanced Measures from DXA and QCT: Fracture Prediction Beyond BMD. Part I (refs on pages 355-575); Part III (refs on page 407).

[H] Mindways QCT Pro hip bone density analysis software incorporated within FRAX App and Online tool https://www.sheffield.ac.uk/FRAX/index.aspx

[I] Cambridge QCT Pro service: (i) Director of Radiology approving opportunistic QCT Pro service & 2015-2019 audit data (ii) Confidential Testimonial from a Cambridge patient (iii) Royal Osteoporosis Society Bone Academy Patient Insight Survey report 2020, page 3.

[J] Denosumab sales. GaBi online, 'Denosumab biosimilar being developed in Australia', September 2018.

[K] Testimonials on Dr Poole's collaborations with (i) Amgen & UCB from the Head of Medical External Affairs at UCB and (ii) collaborations with Lilly, from the International Therapeutic Area Medical Leader in Osteoporosis

[L] L. Lilly Prescriber materials featuring Cambridge hip CBM page 2.