



*National Institute for
Health Research*

The National Institute for Health Research
**Biomedical Research Unit for
Musculoskeletal Disease**

at the University of Sheffield and
Sheffield Teaching Hospitals NHS Foundation Trust



Sheffield Teaching Hospitals
NHS Foundation Trust



Director's Message

Why do we need the NIHR Biomedical Research Unit for Musculoskeletal Disease?

In recent years, changes have been made to the way that health research is funded in the NHS. The National Institute for Health Research (NIHR) was established in April 2006 to carry forward the vision, mission and goals of the Government's health research strategy *Best Research for Best Health*:

to create a health research system in which the NHS supports outstanding individuals working in world-class facilities, conducting leading-edge research, focused on the needs of patients and the public.

The creation of Biomedical Research Units was an important part of this strategy, helping to take the results of medical research out of the laboratory into the hospital clinic.

Bone diseases, such as osteoporosis and osteoarthritis, are increasingly common. Osteoporosis results in increased fracture risk, and both hip and vertebral fractures are associated with increased mortality. As our population ages, hip and knee joint replacements are also becoming more common, as are the problems associated with joint replacement failure. These conditions are creating a clinical and economic burden on society.

Our research spans bone health from childhood throughout life. We are interested in evaluating reasons why individuals do not achieve optimal peak bone mass in early adulthood. We also investigate causes of bone loss and increased fracture risk in the elderly, and the causes and treatment of joint replacement failure.

Funding from the NIHR has allowed us to pursue our goals and we continue to

- drive **innovation** in the prevention, diagnosis and treatment of ill-health
- **translate** advances in medical research into benefits for patients
- provide a key contribution to the UK's **international competitiveness**



Why in Sheffield?

Few, if any, institutes in the UK or Europe have such well established core facilities as we do in Sheffield. In 2009, the University of Sheffield recognised our pre-eminence in the field of bone research by opening the Mellanby Centre for Bone Research.

In 2009, ScienceWATCH ranked the University of Sheffield as the top British institution for research into osteoporosis, and fourth in the world rankings.

ScienceWATCH 1999-2009*

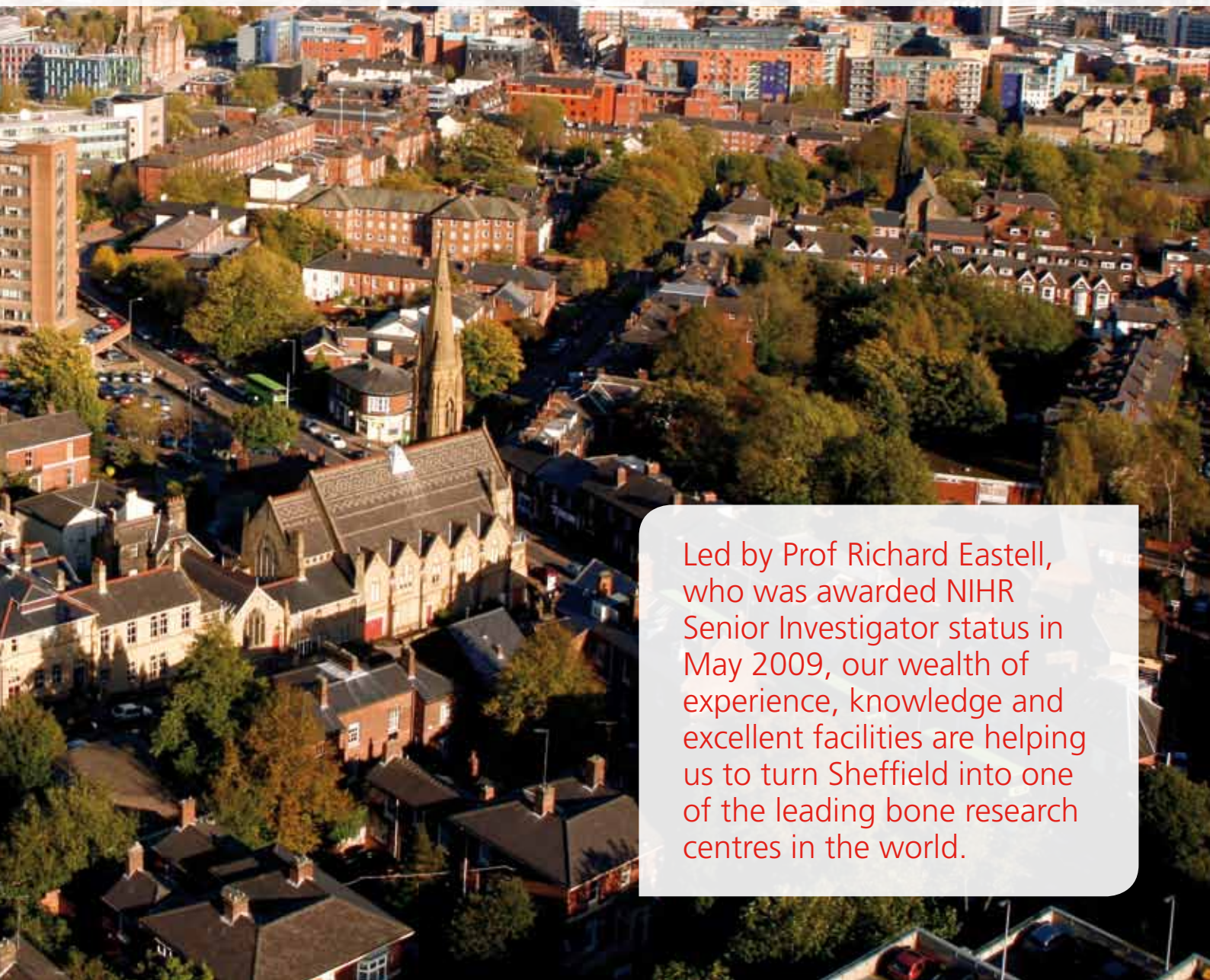
Rank	Institution	Total Cites
1	University of California at San Francisco	20400
2	Harvard Univ.	14932
3	Mayo Clinic	11326
4	Univ. Sheffield	9755
5	Univ. Pittsburgh	7879
6	Columbia Univ.	7002

*(out of 12,241 institutions)



The Metabolic Bone Centre, situated at the Northern General Hospital, is the largest centre of its kind in the UK. The staff here provides award-winning service to patients across South Yorkshire and beyond. We maintain excellent links with NHS consultants, allowing us to translate our research into clinical practice. The Orthopaedic Unit at the Northern General Hospital is also one of the largest in the UK, and is a leading unit nationally for the treatment of complex joint replacement problems.

Right: Profs Jack Martin, Graham Russell, Peter Croucher and Richard Eastell join the vice-chancellor of the University of Sheffield, Prof Keith Burnett, to officially open the Mellanby Centre.



Led by Prof Richard Eastell, who was awarded NIHR Senior Investigator status in May 2009, our wealth of experience, knowledge and excellent facilities are helping us to turn Sheffield into one of the leading bone research centres in the world.

Providing a research infrastructure

Supporting NHS doctors in their research

We are proud of our links with our NHS colleagues, helping them to carry out research in bone disease. We do this by providing them with excellent facilities, and administrative, technical, statistical and editorial support. All new appointments made by the Trust in this area are considered in the light of the likely contribution they will make to our Biomedical Research Unit. We also encourage early-career doctors to pursue their research interests by offering Clinical Research Fellowships, allowing clinical doctors to benefit from our strong support infrastructure.



Editorial Office

Our editorial staff work with researchers to ensure we produce high quality publications, and communicate our research effectively to the wider public. Our two Research Programme Managers have extensive backgrounds in bone research, as well as a solid training in medical writing. They help to prepare research protocols and manuscripts, train staff and students on good writing skills and help in the preparation of slide presentations, conference posters, and external communications.

Lay Advisory Panel for Bone Research (LAPBR)

Our Lay Panel comprises members of the public who have had past experience with osteoporosis or joint replacement surgery either as a patient, relative or carer.

Formed in 2009, the Panel meets once a month to hear about new project proposals from our researchers. They then use their past experiences, as a patient or trial participant, to suggest any improvements they feel can be made to the proposal. The Panel receives regular updates on progress with our research projects and advises on aspects of research such as recruitment issues. Panel members also advise on the dissemination of research findings to the public.

Our investigators agree that the Panel have brought about positive changes to the way they design and run their clinical research projects.





The Academy of
Medical Sciences

MHRA
Safeguarding public health

NHS
National Patient Safety Agency
National Research Ethics Service

The Institute of
Clinical
Research

A new pathway for the regulation and
of health research

Research Governance

The research governance team support the work of the researchers from early on in the study design, in both pre- and post-governance stages. They help prepare the protocol for submission for ethics approval and ensure all necessary study documentation is in place. They closely monitor studies throughout their duration, submitting amendments to ethics as required and maintaining compliance to UK clinical trials regulations, the Research Governance framework and ICH-GCP guidelines. This service ensures that clinical research staff and students in training are supported in the complex environment of research ethics and governance. It also means that researchers can devote more time to recruiting research participants and attending to research study visits.

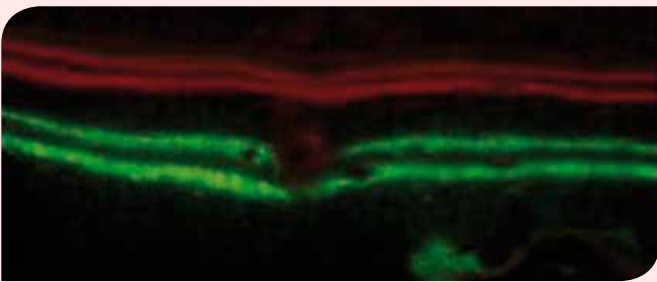
Statistical and Database support

We are supported by the Clinical Trials Research Unit (CTRU), which has been instrumental in setting up web-based clinical trials databases for some of our larger drug studies. Data management support is provided flexibly by the School of Health and Related Research to meet the demands of our projects, so that we are being supported from database and data capture form design through to data interrogation and report requesting.

We have weekly statistics clinics at the Centre for Biomedical Research so that our researchers can benefit from one-to-one assistance from a CTRU statistician.

Our research

We are developing novel bone anabolic agents and new techniques for assessing their efficacy. This includes the development of new bone formation markers and improving methods of detecting bone turnover markers.



We are working with Eli Lilly and Company to examine methods for assessing the timescale and mechanism of parathyroid hormone (teriparatide) as an anabolic therapy.

We are developing the use of fluorescent labels at sites of bone mineralisation, to allow us to study bone formation rates pre- and post-treatment with an anabolic agent.

Our TRIO study, carried out in conjunction with industry partners, is a comparison of three different anti-catabolic treatments currently in clinical use, and thus far has shown that they have different effects on bone turnover markers.

We have found that bone resorption markers decrease early on in treatment, and use of these markers will allow us to assess the effectiveness of new drugs in a much shorter timescale.



Biomedical Research Unit for Cardiovascular Disease



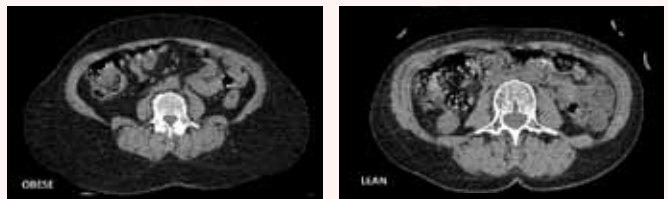
We want to understand the underlying processes which occur during the attainment of peak bone mass, with particular focus on the endocrinological influences. By optimising bone accrual and skeletal health in young adulthood, we hope to reduce the risk of osteoporosis in later life.



We are collaborating with doctors from Sheffield Children's Hospital and the University of Sheffield Academic Unit of Radiology to develop magnetic resonance imaging of trabecular and cortical bone compartments in children and adolescents.

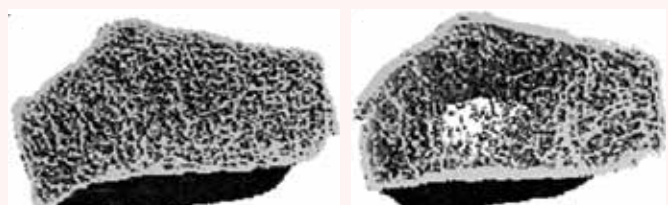
We are also studying the effects of fat on bone, in partnership with the NIHR Biomedical Research Unit for Cardiovascular Disease.

Obese adults have higher bone density than slender adults but are more prone to some fractures.



Different fat compartments (e.g. subcutaneous and visceral) may have different effects on bone.

We are using the XtremeCT to study the geometry and microstructure of bones in relation to levels of the hormones that affect bone turnover, such as parathyroid hormone and IGF-1, as well as adipocyte hormones.

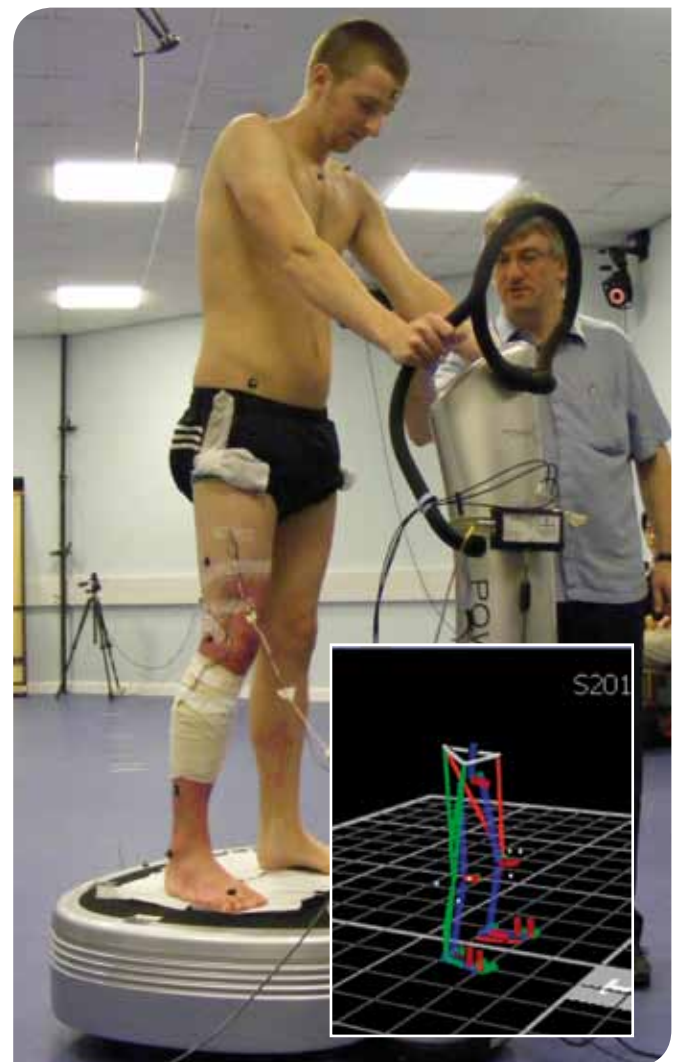
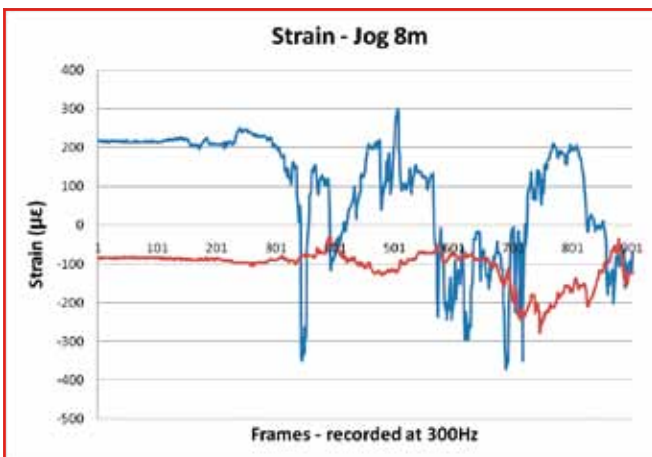
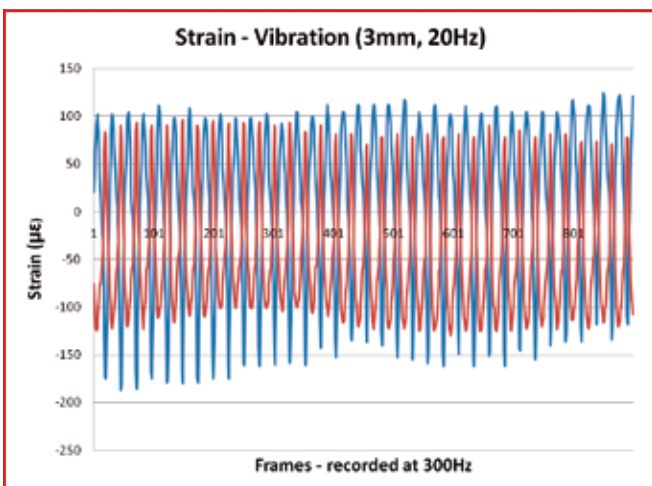


There is some evidence for a beneficial effect of vibration therapy on bone strength, alone or in combination with pharmacological interventions in animals. We are comparing the impact of vibration on bone strain with those caused by normal locomotor activities in man.

There are a number of vibrating plates available, with different mechanisms of action, for example the Powerplate Pro, which has a vertical oscillatory movement. We plan to discover if these plates can help improve bone strength by putting strain on the tibial bones.

We can also measure the transmission of the vibration to other skeletal sites. Eight cameras detect reflective markers fixed on to the study participants, allowing us to reconstruct the movements recorded in fine detail.

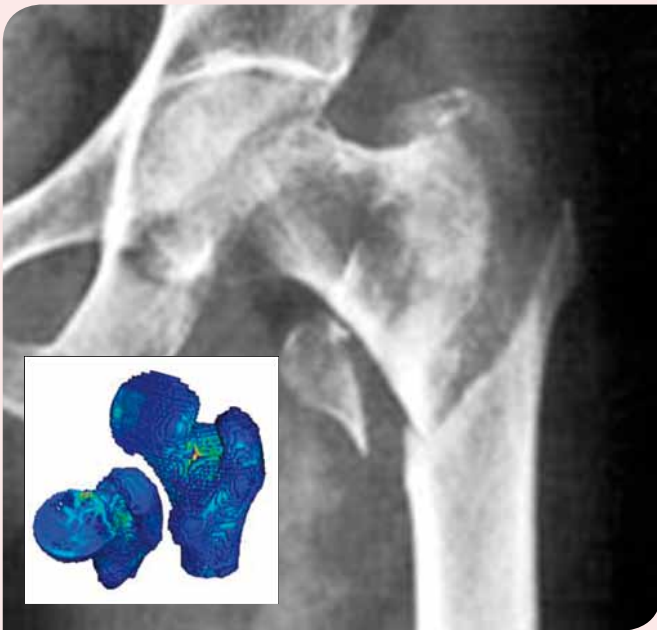
We wish to develop study protocols that will combine optimal vibration therapy with anti-resorptive and anabolic therapies to enhance the skeletal response.



HOLOGIC™

NOVARTIS

We are using structural engineering models and finite element analysis to examine biomechanical determinants of spine and hip fracture, other than low bone density. This will help us to better identify 'at risk' patients.



A number of leading academic institutions are collaborating in this area of research, including University of California, San Francisco, (UCSF); Portland, Oregon; and Boston, Massachusetts.

We have been working with scans of fractured hips provided by Novartis.

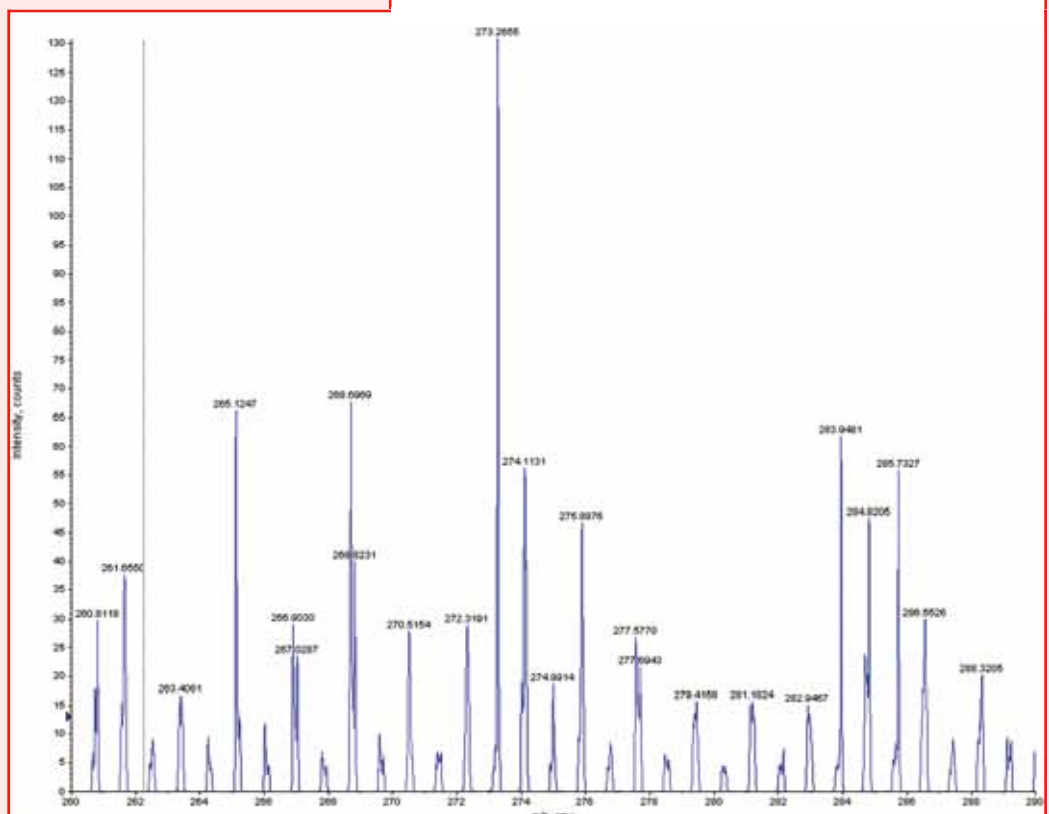
New software, developed with Hologic, allows us to carry out bio-mechanical analyses on 3D models of the hip to predict hip fractures.

Our engineering models of the hip have allowed us to better find patients who will be at risk of hip fractures. This allows us to more effectively target treatment.

Our researchers have better defined a vertebral osteoporotic fracture in comparison to a traumatic fracture, and we suspect that low oestradiol is a major risk factor for vertebral fractures.

We are developing an assay using liquid crystal tandem mass spectrometry to detect very low levels of oestradiol in serum. This technique will enable us to further evaluate the potential use of oestradiol as a predictor of vertebral fracture in women.

An example chromatogram from liquid chromatography tandem mass spectrometry analysis



We are interested in factors associated with the development of osteoarthritis, and are participating in a multi-centre study (arcOGEN) aimed at unravelling the genetic basis of hip and knee arthritis. As part of this we are studying the genetic basis of different hip and knee 'shapes' that associate with arthritis.

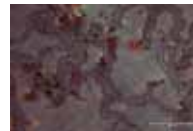


3D computed tomography (CT) reconstruction

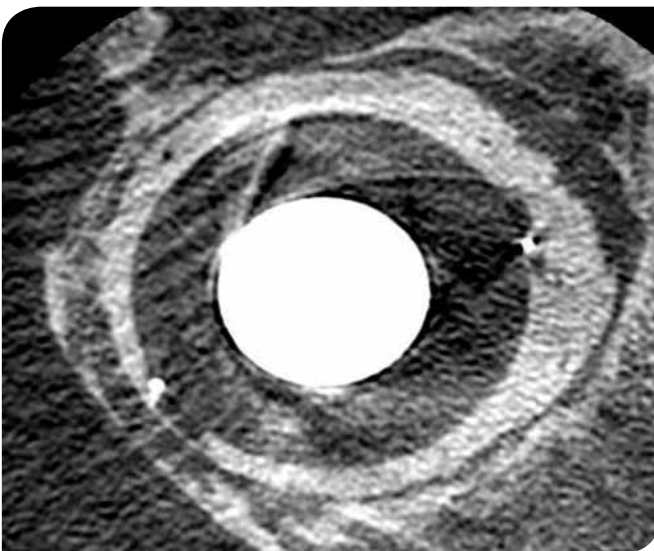
We have developed a software package (SHIPs) that allows us to quickly measure several hip joint morphometric parameters that are associated with future development of osteoarthritis, and we are using this software to identify genetic factors that modulate these patterns.

We have a strong interest in mechanisms of joint prosthesis failure and are conducting a large scale genetic study of the genetic risk factors for prosthesis loosening with national and international partners. We are examining the ways in which the prosthesis interacts with bone cells in collaboration with local industry partners, as well as developing novel imaging and biomarker approaches to the detection and monitoring of treatment in prosthesis loosening.

Some new types of hip replacement associate with high levels of metal ions in the blood. Our current work also examines the potential effects this might have on failure of these prostheses.



We are also examining the effects these ions, for example cobalt, have on bone cells and on general health.



This cone-beam CT image shows aseptic loosening, with osteolysis around the hip socket



Here we can see loosening of the socket component in hip resurfacing

Facilities

Centre for Biomedical Research (CBR)

Situated on the grounds of the Northern General Hospital, the former Clinical Sciences building has been completely refurbished to house the Clinical Research Facility and the offices of both the Sheffield Biomedical Research Units. The Centre became operational in the autumn of 2009, and has allowed the centralisation of much of the units' work.

The ground floor contains the research offices for the Directors, investigators, nursing and support staff, as well as a clinical laboratory and the Biorepository. We also have a seminar room for teaching purposes, study updates and Lay Advisory Panel meetings.

Research facilitators

Our facilitators have a range of experiences which are applied to our clinical research. They provide ultrasound and phlebotomy support for all studies, as well as taking on clerical support for our larger pharmaceutical studies. We have a dedicated IT technician and data entry clerk providing support across all of our studies and advising on the set-up of new studies.



Our **Clinical Research Facility** (CRF) is situated on the first floor of the CBR, conveniently placed above the research offices.

Patients and volunteers enrolled in our studies and clinical trials attend the CRF for all their study visits.

All members of staff are trained in and operate to the UK regulations for clinical trials which incorporate Good Clinical Practice, and our clinical trials nursing team ensure that volunteers receive personalised care throughout their visits.

The CRF has its own sample handling laboratory and freezer storage unit, reducing dependence on the facilities at the Northern General Hospital.

Our experienced **nursing staff** is led by our Senior Research Sister, who oversees all ongoing projects as well as offering practical advice during study set-up. Our research sisters are all assigned to individual projects to ensure a continuity of care throughout our clinical trials. The nursing staff has a wide range of knowledge and experience not only in osteoporosis research but other disease areas also.



The welcoming reception area...



Sample handling laboratory



...with an outpatient waiting room and television.



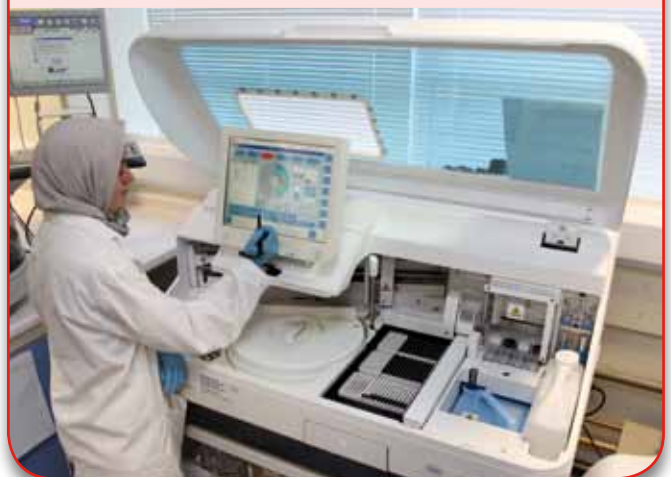
Bed bay with comfortable beds, television and high specification bedside monitoring equipment.



The NIHR funding grant allowed our **Bone Biochemistry Laboratory** to move to a fully refurbished site at the Mellanby Centre, University of Sheffield Medical School. The laboratory is responsible for the measurement of biochemical markers of bone turnover and related tests, such as oestrogens and parathyroid hormone, for all of our clinical trials. It is fitted with a full range of equipment, including five automated analysers capable of analysing up to 200 samples each per day.

- Access II, Beckmann Coulter™
- Vitros 250, Ortho-Clinical Diagnostics
- Vitros Eci, Ortho-Clinical Diagnostics
- Cobas E411, Roche Diagnostics
- Isys, Immuno Diagnostic Systems

Our experienced **laboratory staff** also collaborates with other departments within the University and with external institutions and industry, and provides a bone turnover marker assay service.





Skyscan 1172

The **Bone Analysis Laboratory** is also located within the Mellanby Centre, and we have been able to provide it with additional staff and equipment. This includes a Skyscan 1172, a microCT machine with a camera capable of detecting high resolution X-ray images as the bone specimen is rotated through 360 degrees. Using dedicated software, the images produced can be used to study high levels of detail on bone microarchitecture at the cellular level, and then construct 3D models.

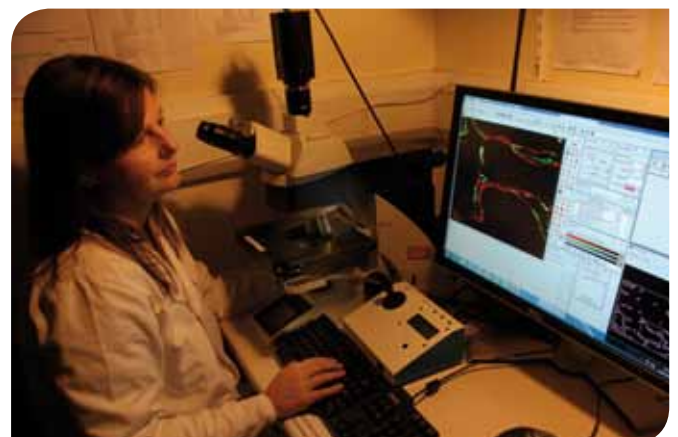
High resolution microCT images can be used in quantitative histomorphometric analysis to measure rates of bone formation. We study trabecular number, thickness and volume; cortical thickness and volume and take bone densitometry measurements.

We have purchased a Leica RM2265 microtome, which we use to prepare thin slices of bone specimens. We employ a range of conventional staining techniques to analyse both decalcified and undecalcified bone specimens.

We also have a dedicated Leica microscope, which is used in conjunction with specialised BioQuant software, to analyse bone formation rates through fluorescent labelling.



Leica RM2265 microtome





Scanning Suite

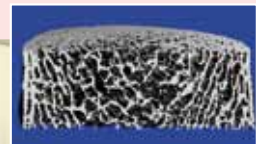
Our specialised scanning suite is conveniently situated in the CRF. It has been equipped with the latest in bone densitometry and imaging equipment, used throughout our studies for analysing bone density and bone structure.

- Discovery A DXA densitometer (Hologic Inc. Bedford, WA, USA)
- XCT2000 pQCT scanner (Stratec Medinzintechnik, Pforzheim, Germany)
- Metriscan phalangeal densitometer (Alara Inc. Fremont, CA, USA)
- DXL Calscan heel densitometer (Demetech AB, Täby, Sweden)
- Achilles Insight heel ultrasound densitometer (GE Medical, WI, USA)
- QUS-2 heel ultrasound densitometer (Metra/Quidel Corp. CA, USA)
- DBM Sonic Bone Profiler (IGEA s.r.l, Carpi, Italy)

Above: Discovery A DXA densitometer

Right: XCT2000 pQCT scanner (XtremeCT) produces high resolution, 3D images of peripheral bone, allowing researchers to look at a cross-section of the cortical and trabecular bone.

Our full-time **scan technicians**, managed by our Research Lead for Bone Densitometry, are trained in a variety of densitometric techniques including dual energy X-ray absorptiometry (DXA), volumetric X-ray absorptiometry (VXA), vertebral fracture assessment (VFA), peripheral quantitative computed tomography (pQCT), high-resolution peripheral quantitative computed tomography (HR-pQCT), radiographic uniformity (RA), dual energy X-ray absorptiometry and laser (DXL) and quantitative ultrasound (QUS).





Biorepository

The Sheffield Biorepository is a joint initiative between the University of Sheffield and the Sheffield Teaching Hospitals NHS Foundation Trust. In 2009 our Human Tissue Act (HTA) license was extended to include a satellite site at the CBR. The Biorepository provides state-of-the-art equipment for the safe storage of biological samples. We currently hold around 200,000 samples from across all of our studies.

This Biorepository also holds samples for the **Sheffield Musculoskeletal BioBank**. These samples are from patients who consent to the use of their tissue for future, as yet unspecified, research projects. We welcome applications from researchers who wish to use these samples. All applications are considered by our BioBank Committee, which comprises representatives from the Biorepository, the STH Research & Development Department, the lay public, clinicians and the NIHR Biomedical Research Unit for Musculoskeletal Disease Management Group.

Our **Biorepository technicians** are responsible for ensuring the facility remains HTA compliant. They rack and catalogue samples, carry out sample handling, and arrange shipment of samples to/from the lab and external collaborators. The conditions within the Biorepository are very carefully maintained, and the Biorepository technicians can view the freezer temperatures in real time from remote locations using a web-based monitoring system.



Training researchers for the future



As part of our world class research, we aim to equip all those who train and work in our unit with expertise that they can take with them into the future.

We offer one year projects to medical students undertaking intercalated BMedSci degrees, giving them the opportunity to undertake a clinical or non-clinical project working with our investigators. We have a number of PhD students, as well as clinical fellows working towards PhDs or MDs.

Our three-tier training programme runs over a two-year cycle, and complements the University of Sheffield research training programmes. It delivers training in basic and advanced aspects of bone biology and bone disease and general research skills. All of our staff and students are encouraged to access the programme and have input into the programme design.



Photos: Staff and students sharing a videolink training session between the Northern General and the Royal Hallamshire sites.



Prof Richard Eastell
Director



Prof Eugene McCloskey
Investigator



Dr Nicola Peel
Investigator



Mr Mark Wilkinson
Investigator



Dr Jennifer Walsh
Investigator



Dr Lang Yang
Investigator



Dr Kath Knight
Manager



Dr Lynne Ferrar
*Research Programme
Manager*



Dr Angela Rogers
*Research Programme
Manager*



Dr Kim Naylor
*Sheffield Musculoskeletal
BioBank Research Manager*



Dr Margaret Paggiosi
*Research Lead for Bone
Densitometry*



Sr Tracey Higginbottom
Senior Research Sister



Jemima Clarke
Research Coordinator



Fatma Gossiel
Laboratory Manager