Institution: Keele University

Unit of Assessment: A3: Allied Health Professions, Dentistry, Nursing and Pharmacy

a. Overview

Keele University has substantially strengthened its research agenda in the field of Health Sciences since 2008. This growth builds on the successes of the multi-disciplinary primary care research group, ranked 5th strongest primary care research grouping in RAE 2008 – leading to membership of the NIHR School of Primary Care (2008–2015) and establishment of the Arthritis Research UK Primary Care Centre-of-Excellence (2008–2013); competitively renewed 2013–2018), combined with strategic investment from the Medical School at Keele (ranked 2nd in Medicine, Sunday Times, 2012). Investment from HEFCE QR and Medical School funds has enabled strategic appointments to underpin growth across biomedical sciences and a wide range of academic clinical disciplines, and to enhance methodological support for applied clinical research, so as to facilitate development of an increasingly strong research infrastructure.

The theme underpinning this multidisciplinary submission, the first by Keele to this subpanel, is a systems approach to chronic disease, ranging across cellular mechanisms and translational medicine to innovative clinical interventions and health services research. The research groups are principally drawn from the Health Faculty's two research institutes: the *Institute for Science and Technology in Medicine* (**ISTM**: biomedical science, medicinal chemistry, applied clinical research and health services research) and the *Institute of Primary Care and Health Sciences* (**IPCHS**: primary care and musculoskeletal research). Through the Faculty Research Committee and Faculty Executive Group, the two Institutes liaise closely on research strategy, capacity development and plans, and on priorities for staff appointments in key areas.

ISTM is a highly interdisciplinary unit with a strong focus on the development of basic technologies in biomedical science, based on collaboration between scientists and clinicians, underpinning translational research in genetics, biomarkers, treatment interventions and disease monitoring, combined with expertise in epidemiology and biostatistics. Its structure fosters the cross-disciplinary integration of engineers, physicists, medicinal chemists, pharmacologists, biologists, clinician scientists and health services researchers and this submission reflects research groups drawn from across that Institute's research themes that include: Applied Clinical Research (including the Health Services Research Unit); Rehabilitation; Neuroscience; Cell and Molecular Medicine, and Tissue Engineering and Regenerative Medicine; this last theme forms the core of a strong submission to UoA15 (General Engineering). As a whole, **ISTM** has seen a 46% growth in research-active clinical/academic staff FTE since RAE2008, supported by academic and clinical appointments in Keele's Schools of Medicine, Pharmacy, Health & Rehabilitation and Nursing & Midwifery, where new research-based posts and promotions have been carefully planned within areas of research strength. Overall **ISTM** has been awarded £21.4 million in new research grants and contracts over the five year period 2008/09 to 2012/13, with a growth in new awards from ~75 to ~125 per year. Postgraduate research student numbers have risen substantially from ~50FTE at the last RAE to ~90 FTE at present.

The **primary care musculoskeletal research group** from **IPCHS** represents the Arthritis Research UK (ARUK) Primary Care Centre-of-Excellence, whose research focuses on the extent, impact, long-term outcomes and primary care management of pain and arthritis. Since RAE 2008, the group as a whole has been awarded £27.5 million in competitive grants, representing a four-fold growth in total grant awards, and a growth in staff FTE of 81%. Grant expenditure during the REF census period has increased by 87%, PGR student numbers have doubled and doctoral awards have increased two and a half-fold. In addition to being the ARUK Primary Care Centre-of-Excellence, the group is a member of the National Institute of Health Research School of Primary Care Research (NIHR SPCR) as a result of its strong performance in RAE 2008. It is a strongly multidisciplinary grouping of allied health professionals (AHPs), epidemiologists, biostatisticians, general practitioners, rheumatologists, and medical sociologists, supported by strong international collaborations, a fully-registered NIHR Clinical Trials Unit, specialist IT and health informatics staff, an active group of research users and an exceptionally strong clinical infrastructure within the NHS. Grant highlights that include the AHP group in primary care as lead or co-applicants include

its Arthritis Research UK (ARUK) Primary Care Centre-of-Excellence (2008–2013, competitively renewed 2013–2018) (£4.7 million), NIHR School of Primary Care (SPCR) competitive grants (£2.75M), 3 National Institute of Health Research (NIHR) programmes, 8 project and 9 fellowship grants (£9.1M), and 4 MRC grants (£1.4M). The research group, its infrastructure staff and the leadership teams of its NHS clinical partnerships are co-located within its flagship purpose-built research centre, forming the largest research grouping within Keele. Its strategic regional and national partnerships with NHS primary care commissioners, GPs and community healthcare providers secure intensive NHS engagement in designing, delivering and disseminating its research, a supportive environment for clinical academics, and strong career pathways to underpin clinical research training initiatives, demonstrated by our innovative development of a cadre of clinical academic AHP posts (**Dziedzic**, **Hill**, **Bishop**, **Holden**, **Konstantinou**). The group includes leadership of the Musculoskeletal Specialism within West Midlands North Comprehensive Research Network (**Dziedzic**), ensuring high-quality delivery of its clinical research. Its more recent leadership of the Primary Care Innovation Unit within the West Midlands Academic Health Sciences Network, which takes **Hill's** StartBack trial as its first exemplar project for NHS roll-out, strengthens its capacity to disseminate and implement research in the NHS and internationally. The impact of its research in advancing health policy and clinical practice and improving patient outcomes is demonstrated by the group being awarded the Queen's Anniversary Prize in 2009 for *Pioneering the early prevention and treatment of chronic pain.*

b. Research strategy

Since 2008, **ISTM** has sought to strengthen its emphasis in the field of applied health research across the board, restructuring its research themes under the focus of chronic disease, and appointing strong clinical leads. A new partnership between **ISTM** and the Arthritis Research UK Primary Care Centre in **IPCHS** has supported creation of a Health Services Research Unit (HSRU), which secures the support of strong methodologists in applied research to underpin this initiative. Keele's strategic decision to align the NIHR Research Design Service (West Midlands) and its NIHR CTU alongside the HSRU has further strengthened this environment.

This over-arching strategy has fostered a faculty-wide, multi-disciplinary, team-based approach to strengthening health research that is organized into three main groupings: (1) **Translational medicine**, (2) **Health services research** and (3) **Primary care management of musculoskeletal conditions**, with significant overlap in leadership and research methodologists, enabling the development of cross-cutting themes (for example rehabilitation, multimorbidity).

1. Translational Medicine:

Our translational research is organised into three main groupings – *molecular medicine*, *medicinal chemistry* and *genetic or biomarker association studies,* with cross cutting methodologies (e.g. whole genome epigenomics, gene control of apoptosis) and health themes (e.g. neuro-degeneration, multiple sclerosis, rheumatoid arthritis, foetal growth and pre-eclampsia).

1.1 Molecular medicine Group: This group is investigating mechanisms involved in the development and therapy of chronic disease, focusing particularly on cancer and neurodegenerative diseases, at the cellular and molecular level. These investigations include translational studies in collaboration with clinical colleagues in Keele, nationally and internationally (*see section e*). We have used functional approaches, including cDNA expression cloning and retroviral insertional mutagenesis to identify, *de novo*, genes involved in the regulation of apoptosis and cell survival (**Williams, Mourtada-Maarabouni** and **Pickard,** >£0.5M *funded by BBSRC, Wellcome Trust, Leukaemia and Lymphoma Research* and *Breast Cancer Campaign*). Current ongoing investigations are concerned with demonstrating the clinical importance of several genes, including long non-coding RNA GAS5, in the regulation of oncogenesis and the response to chemotherapy (**Mourtada-Maarabouni and Williams'** GAS5 2009 *Oncogene* paper cited 33 times in 2013 so far). **Richardson** has focused on the analysis and improvement of anti-cancer chemotherapeutic drugs, particularly those affecting the tumour cell's susceptibility to apoptosis induction. **Farrell** has applied a whole-genome strategy based on the detection of cancer-associated epigenetic changes to identify genes involved in oncogenesis particularly in pituitary tumours where his team have been the first to apply this strategy in this context, (*Faculty of 1000 nominated publication, Endocrinology 2012*), leading to Grand Round invitations to present this

work at NIH and Harvard. He has subsequently broadened the analysis of the role of epigenetic changes to include other chronic diseases and the potential of drugs that modulate epigenetic changes, with new funding from *Tenovus (£50k, prostate cancer)* and the *World Cancer Research Fund (£150k)*. Our *Neurobiology* grouping addresses different aspects of cerebral neuropathology. **Exley** has made key observations on the role of metal ions, particularly aluminium, in the pathology of Alzheimer's disease and other neurodegenerative diseases *(Scientific Reports, 2013) (MRC, EPSRC, Spritzer, £750k)* and **Chen** has focused on the molecular pathology of cerebral ischaemia. We are investigating different aspects of recovery from neurological damage – **Mazzocchi-Jones** focusing on the potential use of stem cells, **Glazewski** (*BBSRC and Wingate Foundation, £350k*) and new appointee **Caruana** on neural plasticity, and **Pickard** on the use of magnetic nanoparticles in gene transfection.

1.2 Medicinal chemistry: Our medicinal chemistry group focuses its research on the design and synthesis of molecules that target specific biomolecules in order to achieve the desired efficacy, based on an understanding of the underlying biochemistry. The recent acquisition of a 400 MHz NMR spectrophotometer (purchased using royalty income from tetrafosmin, a cardiac imaging agent developed at Keele) and various lab upgrades (including a £2M wet lab) have enhanced our facilities, so that the group is able to compete on the international stage. **Bailey** and **Phillips** have prepared a number of indolic targets, including libraries of compounds that have potent anti-malarial properties, and which have been studied by Horrocks et al. (submitted to UoA 5). Heterocyclic targets feature strongly in the research of the group, with **Phillips** preparing several kinase inhibitors, **O'Brien M** synthesizing a number of macrocyclic anti-cancer targets, and **Edwards** focusing on new methodologies to access naturally occurring ring systems of compound families with known medicinal properties. A key area for developing new drugs is the scale-up of synthetic methods, and **O'Brien M** is pioneering the use of continuous-flow technologies to achieve this, with his *Organic Letters* paper being highlighted several times, and among the top 20 most cited papers from that journal for 2010. His flow technology reactor design has been commercialized by 'Uniqsis', 'Cambridge Reactor Design' and 'Vapoutec'. An understanding of the underpinning biochemistry is essential, and fundamental work at the chemistry/biology interface has been carried out by **Morgan**, who has been identifying receptors linked to obesity, and developing drugs that would act as antagonists (over 3,500 citations in total); he led a trans-national (US, UK and Sweden) multidisciplinary obesity group at AstraZeneca, with direct input into board-level decisions on Phase 2 projects of up to £100M). As well as the biological activity of compounds themselves, the transport of drugs to their targets is another key issue, and the **Bailey** group has studied the mechanism of peptide translocation in detail, allowing the design of carrier molecules that can increase the oral bioavailability of a wide range of drugs, and for which international patents have been recently approved. This work is neatly complemented by the percutaneous absorption studies of **Moss**, including collaborative work with the Dermal Technology Laboratory (a company on the Science Park at Keele), where the focus is similarly on developing the pharmacology to improve the ease of drug administration and enhance patient compliance.

1.3 Genetic and biomarker association studies: The interaction between genetic and environmental factors as they relate to clinical phenotype has been an overarching theme of this group, whose research is also characterized by strong national and international collaborations. We have extended the whole genome approach to investigate epigenetic mechanisms in the pathogenesis of rheumatoid arthritis (*with new funding from the Haywood Foundation, >0.5M* **Farrell**, **Fryer, Mattey** and **Jones**) and foetal epigenetics, identifying "gene-signatures" that are predictive of birth weight and other factors that impact on these associations (**Farrell**, **Fryer** and **Jones**). These observations complement those of **Baker** investigating the interaction of diet and micronutrient status in pregnant adolescents, showing that folate deficient diets lead to small-for-gestational-age babies (*Am J Clin Nutrition, 2009*). This complication of pregnancy is also a feature of pre-eclampsia, a serious complication of pregnancy that is hard to predict. **Baker** has led an international group using metabolomics to identify a consistent discriminatory metabolite signature in early pregnancy, (*Hypertension, 2010*) offering insight into disease pathogenesis and promise of a robust pre-symptomatic screening test. This study led directly to 14M media hits, a patent, a spin-out company and a hospital trial (with **O'Brien PMS**) funded by a €6M EU FP7 programme grant. Other examples of gene-environment interactions we have investigated include the influence of smoking on cardiovascular disease in rheumatoid arthritis and the effects of psychological stress, differential gene expression and clinical phenotypic subtypes in chronic fatigue syndrome

(**Mattey**). As lead for the North West of England Multiple Sclerosis Genetics Research group (Keele, Liverpool and Manchester), which is part of the International Multiple Sclerosis (MS) Genetics Consortium, **Hawkins** was a major contributor to the pivotal Genome Wide Association Study in MS (*Nature*, 2011). **Hawkins** and **Strange**, focussing on genes relating to rates of progression in MS, lead the gene-environment studies for Ultraviolet radiation and Vitamin D for the Consortium, working with colleagues in Scandinavia and the USA. With **Fryer** and **Jones**, they have pursued links between genotype and ultraviolet light exposure in a number of chronic conditions.

2. Health Services Research

The Health Services Research Unit (HSRU) was established in 2011 with the purpose of strengthening **ISTM**'s applied clinical research programme. Under its current director (**Davies**) a strategic plan has been developed with a multidisciplinary academic focus on factors affecting the management of long-term and multiple chronic conditions at the primary/secondary care interface (**Roffe**, **Fryer**, **Kadam**). This represents the key challenge for the local health-care economy as well as being a major national priority. The HSRU researches management of complex medical conditions in the community and across the primary/secondary care interface, and plans are in place to expand the NIHR Clinical Trials Unit within the primary care musculoskeletal research group to build on our translational research in chronic conditions and to support the large clinical trials in which **Brunt**, **Hawkins** and **Roffe** are involved.

2.1 Peritoneal dialysis research: The Keele HSRU is now the recognized UK research hub and a leading international centre for applied research into this treatment for complex patients with dialysis in the community, led by **Davies** over many years (*see impact case study*). Multicentre studies led from Keele include PD-CRAFT (NIHR, 43 centres) and with Professor Nick Topley (Cardiff University), the Global Fluid Study since 2002, currently the most comprehensive international cohort study (10 centres UK, Canada and Korea) reporting treatment outcomes (with data analysis led from Keele HSRU: **Lambie**, **Bankart,** *J Am Soc Nephrol,* 2013). During his tenure as president of the International Society of Peritoneal Dialysis (2010–2012), **Davies** facilitated initiation of the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) in association with the Arbor Research Collaborative (Mitchigan, US), a comprehensive international effort designed to optimize the world-wide use of this treatment modality as well as underpinning the national strategy to increase the use of home dialysis care. Funding for this study (currently ~$8M) is from multiple sources including the Canadian Institute for Health Research, National Health and Medical Research Council of Australia, National Institutes of Health (US), **Davies** with Mehrotra, Washington University, $3.7M), Japanese Society for Peritoneal Dialysis and industrial partners.

2.2 Hyperacute and acute stroke research: Our research programme stretches from clinically applied studies aimed at alleviating the impact of stroke using early interventions, i.e. within 24 hours of a stroke, to fundamental modelling studies aimed at elucidating the pathophysiological mechanisms of common neurological impairments. As Clinical Director for the West Midlands Stroke Research Network, **Roffe** has developed a strong research programme designed to test early interventions to improve early recovery from stroke. Recruitment has now completed to SO2S, a national Stroke Network Study led from Keele investigating the impact of early oxygen treatment on recovery from Stroke (**Roffe** chief investigator**,** with **Sim,** HTA, £1.4M, n=8000), and we have evaluated novel rehabilitation interventions to accelerate post-stroke recovery of physical function, with particular focus on the upper limb (**Pandyan, Roffe**, **Hunter**, **Jones, Sim**, joined by new appointee **Stapleton**).

2.3 Chronic disease monitoring and multimorbidity: As society ages the number of people with multiple long-term conditions is increasing dramatically, with important implications for integrated management of multiple conditions and appropriate laboratory monitoring. **Fryer** is co-leading a national research initiative under the auspices of the Royal College of Pathologists (RCP) based on his research findings (with **Jones**) to establish the optimal frequency of laboratory testing of patients with long-term conditions. Keele is the centre for national quality bench-marking of pathology laboratory tests, and augmented by access to well established primary care (with **Kadam**) and pathology databases through the HSRU, Keele is uniquely placed to lead this RCP initiative. The linked theme of near-patient monitoring of chronic conditions includes continued

development of pictogram analysis for menorrhagia (*see impact case study* **O'Brien PMS**) and novel approaches using breath analysis to monitor *Pseudomonas* infection in children with cystic fibrosis (**Gilchrist, Belcher**). Taking an epidemiological approach, we have investigated the impact of multiple chronic diseases on the health and care of older populations led by **Kadam**, in collaboration with WHO collaborating centres in Primary Care, (Netherlands Institute of Health Research, Utrecht) and Evidence-Based Health Care in Musculoskeletal Disorders (Lund, Sweden), NIHR Post-Doctoral Award 2008 (£370K). The finding of shared risk factors between the common comorbidities of cardiovascular disease and osteoarthritis led to the demonstration that use of statins as cardiovascular disease prevention may also protect against the development of osteoarthritis (**Kadam**, **Belcher** *J Gen Int Med, 2013*). Ongoing investigation of the impact of multiple conditions in patients with heart failure and frailty, led by **Kadam**, are underpinned by an NIHR doctoral award (Rushton, £300K*)* and NIHR in-practice fellowships (>£200K).

3. Primary Care Management of Musculoskeletal Conditions

The group's **strategy** is to underpin a shift in the primary care management of osteoarthritis and spinal pain, away from a narrow biomedical focus on disease to a holistic approach that addresses pain and disability in their own right. Unifying themes within this strategy include:

3.1 Understanding the extent, course and impact of musculoskeletal pain over time: combining analysis of well-characterized and long-term cohorts with linked medical record data, the group aims to increase understanding of the extent, course and impact of musculoskeletal and pain-related disorders on individuals' and population health and to provide clinically reliable classifications of musculoskeletal phenotypes that account for fluctuation over time and the effect of concurrent conditions, including treatment response predicted by comorbid pain. Our 6-year follow-up of large population (n=26,625) and clinical (n=2,002) cohorts of older adults with knee, hand and foot osteoarthritis (OA) (MRC Programme grant, £932k,, 2006–2010; ARUK Programme grant, £790k , 2008–2013; **Dziedzic**, **Wilkie**, **Thomas**, and **Muller**, **Bucknall**: NIHR SPCR Postdoctoral Fellowship, £240k) have demonstrated the long-term trajectory of OA pain in the community at the level of the person and by anatomical region, identified key risk factors for onset, and defined clinically important phenotypes to classify sub-groups of OA at highest risk of poor outcome who may benefit from early or additional treatment (erosive hand OA; patellofemoral radiographic change). Prognostic models have been developed to predict the clinical course and long-term impact of joint pain and OA and associated disability (regardless of pain site) to identify those at high risk who may be targeted for interventions. The group has shown that it is feasible to apply simple prognostic tools in primary care at the point of care, and that their systematic use improves accuracy of predicting patient outcomes (**Belcher**, **Thomas**, *JAMA Internal Medicine*). From our analysis of the determinants and outcome of primary care consultation for OA, we have developed new prognostic stratification approaches to improve recognition, assessment, diagnosis, monitoring and management of OA in primary care settings. This modelling work underpins our development of stratified care for OA, including supported self-management approaches, timely interventions to support preventive care, and new models of care to improve long-term outcomes.

3.2 Identifying predictors of poor outcome, developing prognostic models that can support stratification of patients according to risk, and developing/evaluating models of stratified care: We have investigated the prognostic value of biological, physiological, psychological and behavioural markers, and social and work-related factors, across the range of musculoskeletal conditions. We apply novel statistical methods to investigate the inter-relations between different prognostic factors and their cumulative effect over time, to gain a better understanding of their association with health outcomes, identify those prognostic factors that may be modifiable through targeted interventions, and develop these into innovative assessment tools to support clinical decision-making in primary care. We lead the musculoskeletal field in developing practical prognostic and diagnostic tools that can be used in clinical settings to identify modifiable risk factors, and we have linked these to stratified packages of care targeted to specific risk-groups. Through our trial of complex interventions (ARUK: StarTBack Trial, £184k , *Lancet)* and linked implementation study (IMPACT Back, Health Foundation, £4.1M), we have demonstrated that stratified care can be implemented in primary care and physiotherapy settings, leading to significant improvement in clinical outcomes and cost savings, alongside positive changes in practitioners' attitudes and confidence in delivering back pain care (**Lewis**; **Hill** ARUK Lectureship

in AHP, £292k; **Sanders**). Our next step is to develop and test a broader stratified care model, extending the approach beyond back pain to include the older age range and the five most common musculoskeletal problems in primary care – back, neck, shoulder, knee and widespread pain (NIHR Programme Grant, **Protheroe**, **Hill**, **Lewis**, **Sanders**, £1.98M, 2013–2018). In our new cohort (ATLAS) of 600 primary care back pain patients with leg pain and/or nerve root pain (sciatica), we have tested a new standardized clinical assessment and developed optimal management pathways that include clear criteria to identify different patient subgroups (overcoming the ambiguity of sciatic symptoms in the primary care clinical assessment of back pain patients) and identified matched treatment pathways for each subgroup (including a fast-track approach to secondary care). This work has underpinned career development for key staff (**Konstantinou** NIHR AHP Clinical Lectureship (2009–2013), HEFCE Senior Clinical Lectureship, £250k, 2013–2018; Stynes NIHR PhD Fellowship, £257k, 2012–2016) and informed the design of a new pragmatic RCT of 420 patients with sciatica, where distinct subgroups of patients will be identified based on prognostic and diagnostic information and patients will receive stratified treatment matched to their subgroup (shortlisted by the HTA). Finally, within the same NIHR programme in spinal pain, our nurse-epidemiologist **Wynne-Jones** (NIHR Post-doctoral Fellowship, £270k, 2011–2016) is completing a cluster randomized trial (360 patients from 6 GP practices) that tests the effectiveness of a new stepped vocational advice service in general practice (SWAP), providing targeted individualized support to patients with musculoskeletal pain who struggle to maintain work, with the aim of reducing sickness certification and work absence.

3.3 Improving the content of primary care, by designing, delivering and evaluating pro-active, co-ordinated treatments and care pathways: our innovative treatments and models of care address the complex combinations of needs in managing pain and disability, and include pharmacological and non-pharmacological approaches to clinical management and to supporting self-management. We evaluate the clinical and cost effectiveness of new models of primary care, as part of our strategy to improve access to primary care for musculoskeletal patients to receive the right care at the right time. We collaborated with Bristol University to complete the MRC PhysioDirect trial (2008–2011; £265k, **Bishop**, *BMJ*). This compared usual face-to-face physiotherapy care with GP referral to a telephone physiotherapy advice service, where face-to-face treatment was provided only when necessary, in 2,256 consulters to general practice. Whilst the trial demonstrated that PhysioDirect is not more cost-effective than usual care, its cost is within current "willingness to pay" thresholds and the trial intervention showed that PhysioDirect is equally clinically effective and acceptable to patients, and that patients accessed physiotherapy treatment much more quickly, within 7 days compared to 34 days when traditional referral routes were followed. STEMS (**Bishop**, Chartered Society of Physiotherapy £200k) extends this approach to test the addition of a self-referral to physiotherapy pathway to usual GP-led primary care for adults consulting in primary care with musculoskeletal problems. We design and evaluate life-style interventions that may either be condition-specific – e.g. physiotherapist supervised individualized exercise prescription for knee osteoarthritis – or generalizable to multi-morbid chronic disease conditions, e.g. improving adherence to increased physical activity (**Holden**, ARUK PhD Fellowship, £77k). The BEEP trial (NIHR Programme Grant, £2.1M, 2008–2014; 650 patients), now in three-year follow-up, is evaluating the effectiveness of these two approaches to improving physical activity among patients with knee pain. In line with our concern to ensure our research has a rapid impact in improving the quality of musculoskeletal services and patient outcomes, we have developed a brief patient-reported outcome measure (PROM) that can be used to monitor the effect of musculoskeletal care on patient outcomes (**Hill**, RfPB, £174k, 2010–2013) and now plan to develop its extended use across general practice, physiotherapy, rheumatology and orthopaedic settings. (**Hill**, ARUK grant, £65k , 2013–2015).

We investigate the effectiveness of primary care interventions that are commonly used but for which the evidence base is poor, and develop and evaluate new models of care, including novel ways to support self-management with the goal of improving long term outcomes of care. TATE (**Chesterton**, **Lewis**, **Sim**, NIHR RfPB, £263k , 2009–2012; *BMJ*) developed **Chesterton's** laboratory-based research, which evaluated the efficacy of TENS, to assess the clinical and cost effectiveness of a self-management package of treatment that included TENS as an add-on to primary care management in 241 primary care consulters with tennis elbow. The results show large improvements in pain and function in participants receiving primary care management consisting of good information and advice regarding exercise and pain medication. The additional

use of TENS as a self management approach did not provide additional benefit. A series of linked applied clinical studies have been completed. The SMOOTH trial (**Dziedzic**, ARUK, £196k , 2009–2011; *Annals of the Rheumatic Diseases*), a 2x2 factorial design in 257 patients with hand OA identified from a large population survey, comparing hand exercise (vs no hand exercise) and joint protection (vs no joint protection), showed that a joint protection programme aimed to support self-care increases self-efficacy and improves self-reported benefit. The WISE trial (**Protheroe**, *BMJ*) has tested multi-disciplinary approaches to self-care support for chronic disease that build on the existing skills of patients and professionals and include the different ways patients self-manage. Within our NIHR Programme (Optimal Management of OA, 2008–2014), we have developed this approach and tested the feasibility of a model consultation for OA (**Dziedzic**, **Lewis**, MOSAICS), which includes an OA patient guidebook (jointly developed by OA patients and health care professionals), a model GP consultation, which includes systematic recording of quality indicators for OA care, provision of an innovative practice nurse clinic for OA patients and a parallel in-depth study of the process of adoption and implementation (using Normalization Process Theory), in a pilot RCT (8 practices; 525 patients). **Dziedzic** is now taking this work forward into our implementation programme through her NICE Fellowship and link to the Academic Health Sciences Network West Midlands. SUPPORT (**Roddy**, NIHR RfPB, £246k, 2009–2013) is a factorial RCT, which was developed by our Evidence-Based Practice group of AHPs, comparing physiotherapist-led individualized supervised exercise (vs standardized advice and exercise leaflet) and ultrasound guided subacromial injection (vs unguided injection) for patients with subacromial impingement of the shoulder (recruitment completed; in follow-up); EaseBack (**Holden**, HTA pilot £225k 2011–2014) investigates the acceptability of acupuncture for back pain in pregnant women; it has developed the new intervention and is testing the feasibility of conducting a trial in this group of patients. INSTINCTS (**Dziedzic**, **Chesterton**, **Thomas**, ARUK Clinical Studies Group £600k, 2012–2016) compares the clinical and cost effectiveness of local steroid injection or night splinting for carpal tunnel syndrome. In response to feedback from the Research User Group and renewal of the Arthritis Research UK Primary Care Centre-of-Excellence award, the group is now developing a new into early detection and management of inflammatory arthritis. CONTACT (**Roddy**, **Hider**, **Bucknall**, £377k, NIHR SPCR) aims to identify the most effective primary care treatment for acute attacks of gout by comparing two commonly used medicines (low-dose colchicine and naproxen) that have hitherto not been evaluated head to head.

c. People, including:

i. Staffing strategy and staff development

The strategy for appointment of new research staff at Keele University adopts a dual perspective. Core requirements are first identified to ensure maintenance of strength in essential disciplines followed by alignment with strategic institutional growth areas. The adoption of this dual perspective permits both stability and high quality support for growth.

Staff and research capacity development is a priority within **ISTM** and **IPCHS**. All staff are mapped to a core research theme with line management arrangements reflecting disciplinary and research topic focus. Research training and development opportunities are embedded in our core programmes. All newly appointed academics are aligned with dual mentors to develop high-level research skills whilst also supporting them to maintain a balanced portfolio of research and teaching. Each theme lead works with their academic strategy group to set and oversee delivery of the research strategy, review long-term sustainability, skill-mix and individual career trajectories, and set priorities for grant applications. Joint appraisal of clinical academic staff ensures NHS recognition and support of clinicians' academic career development and a balanced clinical and academic work-plan. Individualized career plans are reviewed through the annual appraisal process, which provides a positive and constructive opportunity to address training and other personal development needs, publication plans, grant application plans, conference participation and presentations, and promotion plans. Line management and appraisal arrangements are supplemented by an active programme of exchange visits with international collaborators, personal mentorship (linking with national and international leaders in our fields), and coaching and leadership training opportunities (provided through external consultants and the NIHR Ashridge programmes). A lively programme of external and internal seminars and a series of journal clubs and specialist meetings provide peer-development in the range of topic areas and methodologies important to current research.

The European Commission HR Excellence in Research Award to Keele and the Athena Swan Silver award, (both in 2013) gained by **IPCHS** reflects the high level of performance in providing flexible, family-friendly working arrangements on an equitable basis across all types and levels of staff (e.g. working at home, flexible hours, particularly for those returning from maternity/paternity leave, those with carer responsibilities, those with culturally specific needs, part-time working and job-share arrangements). All staff are supported to participate fully in academic "civic" duties, including peer and grant review activities, research dissemination, conference presentations and active participation on editorial boards and in relevant professional bodies. The two Institutes work collaboratively to secure a ring-fenced bridging fund to enable theme leads to take a long term approach to career development and progression of their key junior and middle rank academic staff, providing protected time for them to develop high quality grant applications. As a result, research groups have supported 4 staff to gain NIHR and ARUK doctoral and post-doctoral Fellowships in Clinical Sciences and Nursing and AHP.

Staff promotions (within Keele and externally) demonstrate our success in supporting career progression among our career-young researchers. Of the staff submitted under UoA3, 4 have been promoted to Professor; 2 to Reader; 5 to Senior Lecturer and 10 to Lecturer since RAE 2008. In addition to support of career advancement at Keele, we have also been supportive of career progression through relocation to alternative employment; 4 staff listed as ECR in 2008 have moved to substantive academic posts in other institutions including Manchester, Warwick, Aston, and Lancaster universities. These former staff members have retained honorary contracts at Keele and continue to collaborate extensively.

ii. Research students

Doctoral projects are integrated and supported through research activity undertaken within each of the themes, and in the case of academic clinicians, are designed to be complementary to clinical training pathways. This level of embeddedness ensures strong peer support for PhD students in addition to structured training. Keele offers a competitive PhD bursary scheme (the ACORN scheme) to attract the brightest young graduates and this has supported significant growth in the PhD cohort to this group (42 PhD and MPhil completions during the assessment period; 92% of our students completing within UKRC targets; 59 FTE PGR students registered for PhDs or MPhils in 2013). Four doctoral students have been supported to gain ARUK or NIHR Clinical Academic PhD Training Fellowships in nursing/AHP. Research students receive a high-quality training that encompasses personal development, transferable, employability, and scientific and subject-specific skills in accord with the Vitae Researcher Development Framework. Doctoral students are required to complete 60 masters-equivalent credits, carefully tailored to individual circumstances and needs, and courses can be accessed from across the University, in line with students' subject-specific needs. Each Research student maintains a Personal Development and Learning Plan (PDLP), which details training requirements and aspirations, along with the preferred routes to acquiring particular skills, reflection on the effectiveness of training undertaken, and research targets and objectives. The PDLP Plan is regularly reviewed with the Lead Supervisor so that specific plans and targets can be reviewed, acted upon and updated as appropriate. It is also supported by ring-fenced funding for conference attendance, additional training and research costs.

d. Income, infrastructure and facilities

Research grant income in the REF period amounts to over £8 million. The quality of our research and its importance and relevance to health providers in identifying potential innovations at bench-side and filling the second gap in translation is reflected in the range of funding bodies that support the research represented in this submission (NIHR, ARUK, MRC, BBSRC, Wellcome, EC FP7) and the impact of our research dissemination. An active research user group (RUG), with over 50 members of the public and supported by two staff who are themselves users of musculoskeletal health care services, ensures that our research is shaped by patient priorities. RUG members support all aspects of the design, delivery, interpretation and dissemination of our work. A dedicated team leads our strategy to support dissemination and implementation of our research. Our Intellectual Property Rights (IPR) Policy secures free and open access to our research IP to promote its rapid dissemination by health providers nationally and internationally, and where appropriate support commercial exploitation of research findings.

Our research and infrastructure staff are co-located within the Guy Hilton Research Centre (with

combined facilities for near-patient studies and laboratory work), the Life Sciences building laboratories (including animal facilities) and the dedicated, purpose-built offices at the gateway to the campus (HSRU and the Primary Care Sciences Research Centre) – the last resulting from significant investment from Medical Charities such as the Wellcome and Dunhill Trusts. A strong and established NHS infrastructure supports delivery of all the applied research, through leadership of the R&D Office at the University Hospital of North Staffordshire (**Fryer**) and the Primary Care Research Network (PCRN-CE, Hughes, **Dziedzic**) and the joint research strategy held with our regional NHS partners in primary and secondary care. 83% of the general practices in our region are accredited as "Research Ready" by the Royal College of GPs (n=231) and Keele research makes a significant contribution (80%) to overall recruitment in our region of PCRN-CE (n=64,000 since 2008). Innovative techniques to support patient recruitment to research, developed by our research teams, include automated recruitment and data collection systems at the point-of-care. Members of our group have undertaken secondments to the NIHR (Hughes) to support set-up of the Clinical Research Networks and national development of streamlined approaches to research governance such as the Research Passport scheme.

e. Collaboration and contribution to the discipline or research base.

i. Research collaborations

ISTM members returned to this submission have an expanding international profile with active exchange networks promoting two-way transfer of researchers, students and know-how within the EU FP6 funded EXPERTISSUES European Network of Excellence, the EU FP7 funded schemes EU/China HYANJI NETWORK (led by Keele), Marie Curie Initial Training Network MAG(NET)IC FUN (led by Regensburg University), BIODESIGN (led by Uppsala University), GENODISC (led by University of Oxford), INFRAVEC (led by Imperial College London), EATS (led by Plant and Food Research, NZ and hosted at ISTM), MYJOINT led by Keil Germany and a Marie Curie Training Programme (Alea Jacta EST). Submitted staff also increasingly contribute to leadership of international collaborative clinical studies, including the €6M EU FP7 programme grant evaluating biomarkers for pre-eclampsia (IMPROvED, **Baker**), the $8M international Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) in collaboration with Arbor Research Collaborative, Michigan (**Davies**) and the International Multiple Sclerosis Genetics Consortium, **Hawkins**. Other international collaborations include: **Farrell** with the Faculty of Biotechnology and Food Technology at the TUAF University in Vietnam (Honorary Visiting Professorship in 2011); **Fryer** with Dr Carmel Hawley, University of Queensland Brisbane, Australia, on skin cancer predictors in renal transplant patients; **Williams** with the University Kebangsaan, Kuala Lumpur, Malaysia – Dr. Salmaan Inayat-Hussein, Faculty of Allied Health Sciences on apoptosis control by styryllactones (funded by the Wellcome Trust International Research Development Award with GKT School of Medicine, London). **Glazewski** with (a) the Nencki Institute, Warsaw, Poland – Prof. Malgorzata Kossut, Department of Molecular and Cellular Neurobiology, on learning induced plasticity of murine barrel cortex (funded by Wellcome Trust), (b) Dept of Cytology and Histology Institute of Zoology, Jagiellonian University, Krakow, Poland, Professor Elzbieta Pyza, on synaptic changes during circadian rhythm and (c) the Carnegie Mellon University, Pittsburgh – Prof Alison Barth, Department of Biological Sciences, on mechanisms of plasticity in the barrel cortex (funded by the Carnegie Mellon University and the Physiological Society); Baker with the Chongqing Medical University, China, and with the University of Auckland. **Hawkins** and **Strange** with the Broad Genetics Institute, Boston (Harvard/MIT) - Dr Phil de Jager, on auto-immune loci in multiple sclerosis, funded by the National Institutes for Health, *USA*. **Davies,** collaborative research programmes with: Profs Qian and Ni, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai; Prof. David Johnson, University of Queensland, Brisbane, Australia; Dr Raj Mehrotra, Washington State University, US.

Each of the primary care musculoskeletal research themes (**IPCHS**) described here attracts world-leading collaborations that are strengthened by Keele visiting professorships. In our Osteoarthritis programme, collaborators from Sweden (Petersen: Lund University), Australia (Blyth: University of Sydney; Menz: LaTrobe University), have been made Keele Visiting Professors to support development of consensus definitions for a range of musculoskeletal disorders, and international comparisons of the course, impact and prognosis of these conditions using electronic health records. They provide crucial expertise in musculoskeletal epidemiology, public health epidemiology and multi-morbidity, facilitate mutual use of data resources, and provide training

opportunities for junior staff. Close collaborations with the University of Washington (Von Korff & Cherkin), University of Southern Denmark (Albert, Mørso), and University of Oslo (Grotle, visiting professor) have enabled research into the international generalizability and implementation of the STarTBack screening tool in Europe and the US. We collaborate with the other leading departments of Primary Care, including Bristol (MRC Physio Direct), Oxford (CONTACT) and Birmingham (West Midlands CLAHRC) on novel primary care intervention studies, and with UEA on stroke rehabilitation (MRC/NIHR FAST INdiCATE Trial).

ii. Contributions to the discipline and research base

Outstanding contributions made to their discipline in 2013 were recognised by the awards to **Baker** of a National Distinguished Professorship by the Chinese Government and to **Davies** the International Distinguished Medal by the US National Kidney Foundation in recognition of his research and presidency of the International Society of Peritoneal Dialysis (2010-12). **Farrell**, **Davies** and **Williams** have published invited reviews for *Nature Endocrinology, Nature Nephrology* and *Nature Reviews Cancer*, respectively. A recent independent bibliometric analysis (Leiden University) showed that 36% of **IPCHS** publications are in the top 20% of most highly cited papers in the world. 44% of that output produced between 2008 and 2011 includes international collaborators and achieved a mean normalized citation score of 2.1, placing the group well ahead of the world average. We hold multiple **leadership roles** with:

(a) key funders in our fields: *NIHR* and *NIHSCR* funding committees: **Bankart**, **Sim**, **Lewis**, **Thomas**, **Roddy, Kadam**; *National Institute for Cancer Research Prostate Cancer Collaborative*: **Williams**; EPSRC College (including grant review panel chair): **Bailey**; Steering Group for £21m HEFCE National STEM Project: **Bailey**; *REF 2014* sub-panel vice-chair: **Sim**; and

(b) key professional and editorial bodies: Fellow of *Royal Society of Edinburgh*: **Bailey**; *NICE Technology Appraisal* (currently committee D): **Jones**; *NICE Fellowship in Musculoskeletal Therapies*: **Dziedzic**; National Chair of *Nervous System Disorders specialty group committee* for *NIHR* and *UK CRN*, 2008–12: **Hawkins**; Clinical Director for *West Midlands North NIHR CLRN* (2010–14): **Hawkins;** Musculoskeletal Specialty Lead for *West Midlands North NIHR CLRN* (2010–14); **Dziedzic**; *Royal College of General Practitioners*: **Protheroe**; *British Society of Rheumatology*: **Dziedzic**, **Roddy**, **Hider**; *Chartered Society of Physiotherapy*: **Bishop**, **Dziedzic**, **Hill**, **Holden**, **Konstantinou**; *Society for Academic Primary Care*: **Protheroe**; *Scientific Advisory Committee of Clinical Practice Research Datalink* (MHRA): **Kadam**; *MRC College of Experts* 2006–9: **Williams**; Chair of the *British Society for Psychosomatic Obstetrics, Gynaecology and Andrology* and *International Society for Premenstrual Disorders*: **O'Brien PMS**; Secretary, *Society of Research in Rehabilitation*: **Pandyan**; Abstract Secretary, *Physiotherapy Research Society* and hub leader, *Allied Health Professionals Research Network*: **Hunter**; Representative of the EPSRC Skin Forum on the All Party Parliamentary Group on Skin, 2008–10 and editor for *Journal of Pharmacy and Pharmacology* themed issue on percutaneous absorption: **Moss;** Editor-in-Chief, *Obstetrics, Gynaecology and Reproductive Medicine*: **Baker**; Associate editor *Peritoneal Dialysis International* and Subject Editor (dialysis) for *Nephrology, Dialysis, Transplantation*: **Davies**; Senior Editor, *Endocrinology, Diabetes & Metabolism Case Reports*: **Farrell**; Associate Editor, *Physiotherapy Theory and Practice*: **Sim**. All our senior academics routinely undertake PhD examining, peer-reviewing and commissioned editorials for major journals, provide plenary invited lectures at major international conferences, have editorial board memberships and chair Trial Steering Committees and Data Monitoring and Ethics Committees for national studies (e.g. **Sim**, **Lewis**).