Institution: University of Leeds		
Unit of Assessment: 12		
Title of case study: Advanced Pre-clinical Simulation Methods Enabling the Development of Longer Lasting Total Joint Replacements		
Period when the underpinning research was undertaken: 2001–2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
John Fisher	Professor	01/08/1993 – date
Louise Jennings	Teaching Fellow, Research Fellow, Senior Research Fellow, Associate Professor	01/10/2000 – date
Todd Stewart	Research Fellow, Teaching & Research Fellow, Lecturer, Senior Lecturer,	01/08/1998 – date
Sophie Williams	Research Officer, Research Fellow, University Research Fellow, Senior Lecturer, Associate Professor, Professor	01/10/2002 – date
Claire Brockett	Research Assistant/Officer/Fellow, NIHR Research Fellow, University Academic Fellow, Associate Professor	01/04/2005 – date
Mazen Al-Hajjar	Research Fellow	01/10/2010 – 11/01/2019
Carol Bell	Research Fellow	01/02/2000 – 10/09/2004
Abdellatif Abdelgaied	Research Fellow	01/07/2012 – 31/07/2019
Tony Haythornthwaite	Graduate Bioengineer	10/09/2012 – 31/03/2014
Period when the claimed impact occurred: 2014 – 2020		
Is this case study continued from a case study submitted in 2014? No		

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

Since 2014, new pre-clinical simulation methods and equipment for replacement hip joints have been developed and commercialised in collaboration with industry partner Simulation Solutions. A new international standard for pre-clinical assessment of hip prostheses (ISO14242-4) has been developed, approved and adopted. This provides, for the first time, a recognised approach to evaluating hip implant designs and materials that simulate variation in surgical translational and rotational positioning, which leads to edge-loading on the joint replacement. New products developed using our advanced simulation methods by our industry partners DePuy Synthes, Invibio, and Mathys and demonstrating lower wear under real world conditions have benefited over 300,000 patients every year (approximately 10 percent of the global market).

2. Underpinning research (indicative maximum 500 words)

The starting point for this research programme in 2001 was the global clinical need for longer lasting and lower wearing total replacement hip and knee joints. These improved prostheses can result in lower revision rates in the longer term (10 to 30 years) for an active ageing population with expectations of 'fifty active years after fifty'®.

State-of-the-art pre-clinical joint simulation technology prior to 2001 represented a single activity standard for a normal walking cycle, described in the first international standard published in

2001 that was based upon our previous research. These standard simulations were able to generate predictions for the average wear rates found in the general population. They did not replicate the variation in conditions that can lead to deterioration and the variation in function and higher wear rates that result in the need for revision in individual patients.

Since 2001, our research programme has developed more advanced systems and methods to simulate different clinical conditions. These include the effect of variations in surgical positioning (including combinations of translational and rotational positioning), resulting in edge loading in the hip joint bearing and the effect of variations of different activities, alignment and soft tissue reconstruction in the knee joint. These methods have been subsequently adopted by industry.

In the hip: In 2001 we described that in alumina ceramic-on-ceramic bearings, simulation of dynamic microseparation of the centres of the bearing and replicating edge loading conditions led to stripe wear and higher levels of wear found clinically in some patients [1]. We went on to investigate the effect of edge loading in ceramic matrix composite, metal-on-metal, and polyethylene bearings. We progressed this to investigate the causes of edge loading and the independent effects of the inclination of the cup and the medial lateral offset [2]. More recently, in 2017, we published on the combined effects of both inclination and offset on the bearing mechanics and function, the level and severity of separation, and edge loading. This work demonstrated a synergistic effect with increased levels of inclination combined with increased offsets producing higher levels of separation (>2 mm), producing more severe edge loading and bearing damage, and further increases in wear [3].

In the knee: In 2005 we created new experimental simulation systems and methods for the tibial femoral joint and reported on the effect of different kinematics on the wear of conventional polyethylene [4]. This showed that increased internal external rotation resulted in increased wear. We progressed this work in 2007 to develop simulations that showed abnormal abduction and lift off also increased wear [5]. More recently, our experimental simulations have been combined with advanced computational simulations to predict wear in cross-linked polyethylene in knee prostheses [6]. The computational methods have been used to simulate contact mechanics and wear for different prostheses designs and for different femoral bearing materials.

The research was undertaken with collaborators in the University of Leeds Faculty of Biological Sciences (Ingham and Tipper (UoA 5) [1, 2]), and in the University of Denver (Komistek [5]). Publications 1, 3, 4, and 6 also have industry collaborators as co-authors. Prior to leaving the University, **Al-Hajjar**, **Abdelgaied**, **Bell** and **Haythornthwaite** contributed to the original research [2–6] as part of **Fisher**'s research group in the School of Mechanical Engineering.

The underpinning collaborative research work has been supported continuously by EPSRC since 2001, and has included Platform grants, Portfolio Partnership funding, and funding for the Medical Technologies IKC and Centre for Innovative Manufacturing in Medical Devices (see EPSRC 'Grants on Web').

External recognition to Professor John Fisher:

- CBE for Services to Medical Engineering 2012
- UK Biomaterials Society President's Prize 2013

External recognition to the Institute of Medical and Biological Engineering:

- Queen's Anniversary Prize for Higher Education 2011

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

[1] Stewart T, Tipper JL, Streicher R, Ingham E, and Fisher J. Long-term wear of HIPed alumina on alumina bearings for THR under microseparation conditions. *Journal of Materials Science: Materials in Medicine* 12, 1053–1056 (2001). https://doi.org/10.1023/a:1012802308636

[2] Al-Hajjar M, Fisher J, Williams S, Tipper JL, and Jennings LM. Effect of femoral head size on the wear of metal on metal bearings in total hip replacements under adverse edge loading conditions. *Journal of Biomedical Materials Research, Part B: Applied Biomaterials* 101B, 213–222 (2013). https://doi.org/10.1002/jbm.b.32824

[3] O'Dwyer Lancaster-Jones O, Williams S, Jennings LM, Thompson J, Isaac GH, Al Hajjar M, and Fisher J. An *in vitro* simulation model to assess the severity of edge loading and wear, due to variations in component positioning in hip joint replacements. *Journal of Biomedical Materials Research, Part B: Applied Biomaterials* 106, 1897–1906 (2018). https://doi.org/10.1002/jbm.b.33991

[4] McEwen HMJ, Barnett PI, Bell CJ, Farrar R, Auger DD, Stone MH, and Fisher J. The influence of design, materials and kinematics on the *in vitro* wear of total knee replacements. *Journal of Biomechanics* 38, 357–365 (2005). https://doi.org/10.1016/j.jbiomech.2004.02.015

[5] Jennings LM, Bell CJ, Ingham E, Komistek RD, Stone MH, and Fisher J. The influence of femoral condylar lift-off on the wear of artificial knee joints. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine* 221, 305–314 (2007). https://doi.org/10.1243/09544119JEIM215

[6] Brockett C, Abdelgaied A, Haythornthwaite T, Hardaker C, Fisher J, and Jennings LM. The influence of simulator input conditions on the wear of total knee replacements: An experimental and computational study. *Proceedings of the Institution of Mechanical Engineers, Part H: Journal of Engineering in Medicine* 230, 429–439 (2016). https://doi.org/10.1177/0954411916645134

All of the above journals are internationally recognised with rigorous review processes and international editorial boards. The quality of the underpinning research being at least 2* is demonstrated by all six references.

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

Simulation equipment, methods and standards

Fisher and **Jennings** have a long-standing collaboration with the company Simulation Solutions. Letter [A] corroborates that since 2013 the company has worked with **Fisher** and **Jennings** on "the advancement of novel simulation methods and systems and the development of simulation equipment". Since 2013, the company has "invested in the design and new product development of advanced equipment including new six-axis electromechanical hip joint simulators EM13, 14, 16 and 17 and six axis electromechanical knee joint simulators", and Simulation Solutions have "sold this novel simulation equipment and provided services and supported the use of these simulators in UK, Europe and Asia to global industry and research institutions". Since 2013, Simulation Solutions has "sold approximately 300 stations of simulator capacity with a value of around £15M, representing over 50% of the global market", with the bulk

of these sales being in Asia where "Simulation Solutions Ltd and the University of Leeds have worked together to raise levels of awareness and understanding of the need for more rigorous testing standards".

In this period, **Fisher** and **Jennings** furthermore applied their research to initiate and author the new international standard [B] for pre-clinical assessment of total hip prostheses (ISO 14242-4), enabling wider use of the novel simulation methods to evaluate and demonstrate reduced wear under real world conditions and to improve the longevity of joint replacements under development. Published in May 2018, the new standard has been approved and adopted globally to evaluate newly developed hip prostheses prior to CE mark approval. Letter [A] confirms that Simulation Solutions supported the work of **Fisher** and **Jennings** in developing this standard, and in pursuing it to final approval and adoption. **Jennings** also chaired the ISO standard sub-committee for Bone and Joint Replacements (ISO/TC 150/SC 4) from 2012 to 2020 [B].

Improved products and new product development

Since 2013, the University has applied its distinctive experimental simulation methods and systems, which subsequently formed the new standard, in collaborative research to support new product developments with implant manufacturers DePuy Synthes, Mathys, and Invibio to reduce wear (under adverse real-world conditions) and improve the longevity of new joint replacements. We provide direct evidence through our cited industrial collaborations of our research impacting on over 300,000 joint replacement implants per year, more than 10% of the global market.

DePuy Synthes: Letter [C] corroborates the benefit of the collaborative research with the University since 2013, and gives two examples:

- The continued sales of ceramic-on-ceramic bearings and the increased sales of ceramic femoral heads for hip prostheses. In REF2014 we reported sales by DePuy of approximately 50,000/annum ceramic composite femoral heads. Letter [C] estimates sales now at over 100,000 per year, a two-fold growth in sales of ceramic femoral heads since 2013. This addresses the increased clinical use of ceramic femoral heads by the orthopaedic community in the UK as reported by UK National Joint Registry [D].
- The development and launch to the market of the ATTUNE knee system in 2013, supported by University of Leeds research. As of March 2020, more than 950,000 ATTUNE knee implants have now been provided for patients around the world [C, E].

In June 2015, DePuy Synthes opened their new global R&D facility in Leeds, providing over 500 skilled jobs [C, F]. Letter [C] states that "together with the University of Leeds, [this facility] maintains the Leeds City Region as a global centre of excellence for technology innovation in orthopaedic implants". This collaboration and centre of excellence forms part of the Leeds City Region Med Tech Hub described in the UK Industrial Strategy, Life Sciences Sector Deal 2, 2018 [G]. Letter [C] confirms "Over 40 Leeds graduates and PhDs work for DePuy Synthes worldwide."

Mathys: University of Leeds collaborative research with Mathys has directly supported the development and manufacture of their new ceramic matrix composite hips Ceramys and Symarec. Letter [H] corroborates the importance of **Fisher** and **Jennings** research in "determining the strategic direction of our new product developments", and "generating essential evidence for dossiers to gain product approval", and notes that "Mathys currently sell or supply approximately 50,000 ceramic hip joints every year".

Invibio: Since 2013 the University of Leeds has worked closely with Invibio to support the development of their novel all-polymer knee system, undertaking all pre-clinical tribological simulations. Letter [I] confirms that "The University of Leeds has been the research and simulation partner of choice", and that the research "has been critical in determining the strategic direction of the new product development".

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

[A] Letter from the Managing Director, Simulation Solutions, Stockport, UK, 14 February 2020.

[B] Letter from the Committee Manager of ISO/TC 150/SC 4, International Organization for Standardization (ISO), 27 October 2020.

[C] Letter from the Group Manager Tribology, DePuySynthes, Leeds, UK, 18 March 2020.

[D] UK National Joint Registry, 15th Annual Report 2018: https://www.hqip.org.uk/wp-content/uploads/2018/11/NJR-15th-AR-Prostheses-used-in-joint-replacements-2017.pdf

[E] 'DePuy Synthes ATTUNE® Knee Surpasses 1 Million Patients Implanted Worldwide', DePuy 23 June 2020 Press Release, https://orthocg.com/depuy-synthes-attune-knee-surpasses-1-million-patients-implanted-worldwide/, accessed 21 October 2020.

[F] 'Leading the Way in Orthopaedics Innovation', Johnson and Johnson Press Release, 4 June 2015, https://www.jnj.com/our-company/leading-the-way-in-orthopaedics-innovation, accessed 26 August 2020.

[G] UK Industrial Strategy, Life Sciences Sector Deal 2, 2018, https://www.gov.uk/government/publications/life-sciences-sector-deal, accessed 15 June 2020.

[H] Letter from the Head of Research & Manufacturing Ceramics, Mathys European Orthopaedics, Mörsdorf/Thür, Germany, 13 March 2020.

[I] Letter from the Head of Medical & Research Development, Invibio Biomaterials Solutions, Thornton-Cleveleys, UK, 24 February 2020.